

# 6<sup>th</sup> International Conference Clinical Cancer Prevention 2010

with Consensus Conference on Chemoprevention of Breast Cancer

18 - 20 March 2010, St.Gallen/Switzerland

## Conference Summary

**6<sup>th</sup> International Conference on Clinical Cancer Prevention (SG-CAP-2010),  
St.Gallen/Switzerland, 18 – 20 March, 2010 (Corr. Version of 4 April 2010, HJS)**

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### Abstract

Close to 200 experts and delegates from 33 countries participated at the recent 6<sup>th</sup> international conference on “Clinical Cancer Prevention” at the newly built Einstein Congress facility in St.Gallen/Switzerland. This 6<sup>th</sup> biannual meeting of its kind in Europe since the millennium year 2000, besides general scientific questions and problems such as infection and cancer, was predominantly focused on primary – and there mainly pharmacologic – cancer prevention (hitherto called chemoprevention), and this especially in breast and prostate cancer. The conference ended with an interesting first (?) international consensus panel on pharmacologic prevention of breast cancer. The meeting was organized by Professor Florian Otto, MD and Prof. Hans-Joerg Senn, MD, both from the Tumor- and Breast Center ZeTuP St.Gallen and from St.Gallen Oncology Conferences, and was co-sponsored and/or supported by ISCaP (Internat. Society of Cancer Prevention), ESMO (Europ. Society of Medical Oncology), ESO (Europ. School of Oncology), EACR (Europ. Assoc. of Cancer Research), ASCO (American Society for Clinical Oncology), Susan B. Komen Foundation for the Cure as well as by the Swiss Cancer League and the regional Cancer League of St.Gallen-Appenzell.

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### **Session 1: Cancer Prevention and Health Politics: Economic and other Controversies**

**Thomas Szucs**, well known epidemiologist from Zuerich University/Switzerland, and newly elected chairman of the board of the largest private Swiss health insurance system, was reminding the cancer prevention community about the excessively rising health expenditures, especially in the field of medical oncology, creating per se a political and economical environment, favorable to exploring new avenues of realistic cancer prevention research and reimbursement experiments. His contribution evoked hopes, that private and also state health insurance companies would join the academic community in new and attractive cancer prevention efforts.

**Bruce Hillner** from the Virginia Commonwealth University in Richmond/USA reviewed the optimal allocation of resources for achieving cancer risk reduction. He noted that in low-income countries, new ways of primary prevention benefits have the greatest economic return because the benefits to cancer incidence are linked with other medical conditions such as the prevention of uterine cervical malignancy with the papilloma virus vaccine or the Hepatitis B virus vaccine. Tobacco control affects lung and other malignancies as well as benign lung disease and cardiovascular disease. Tobacco control via taxation and the use of social engineering have been beneficial across a spectrum of affluence. In high-income countries over the past 20 years there has been an explosion both in the demand for and the cost of new cancer therapies, as well as growth of the demand for and utilization of radiation therapy modalities. Cancer drugs are now the largest class of pharmaceuticals in terms of

annual expenditures worldwide, and new drugs, that are highly effective (such as trastuzumab, imatinib and rituximab), have strained health department budgets or are simply not affordable to many populations. It is not clear whether the use of genomic profiling and biologic imaging such as PET scanning will lead to more selective use of newer, expensive therapies or not. Additional expertise in palliative care will be necessary to stem rising costs while expanding benefits to as many individuals as possible.

**Franz Porzsolt** from the University of Ulm/Germany reviewed lessons learned from existing cancer prevention programs. He noted that the demand for preventive services always exceeds the available resources, and stressed the need to identify the correct criteria to allow optimal evaluation of the costs and benefits of preventive services offered. Behavioral changes are widely advocated for reduction of the incidence of breast cancer, but there are no data yet available to confirm the final epidemiologic impact of these recommendations. He also emphasized that we should distinguish structural markers of disease such as histology or lesion size from functional markers of outcome such as quality of life and survival. He also noted that many cancer sites may have subsets of self-limiting disease, which may become apparent when there is a discrepancy between observed cancer incidence and mortality. He urged that molecular profiles of early stage cancers be correlated with the clinical course and treatment outcomes, and he also made an appeal that risk factors for breast cancer be reported to national data bases by doctors who offer breast cancer screening in order to interpret correctly the outcome of the screening.

## Session 2: Cancer Prevention: The Scientific Base

**Barbara Dunn** from the National Cancer Institute in Bethesda/MD, USA reviewed biomarkers for early detection and surrogate endpoints in breast cancer prevention trials. She defined useful markers as those that are subject to modulation. They are relatively easy to obtain and quantify, and have biological meaning, that represent steps in the carcinogenesis pathway. The ideal biomarker in early phase trials can inform the prioritization of large trials, that measure clinical outcomes. Appropriate trials with validated biomarkers as endpoints should promote faster decisions regarding which targeted preventive agents to pursue. Biomarkers, when fully developed, could become useful in distinguishing indolent from aggressive cancers and prevent over-treatment. Biomarkers in current phase 2 chemoprevention trials have been used to demonstrate the synergistic action of multiple agents possibly allowing lower doses of preventive agents with less attendant toxicity.

**Eugene Gerner** from the University of Arizona, Tucson/USA reviewed the use of polyamines as both biomarkers and targets for chemoprevention. Increased polyamine synthesis and inflammation have long been associated with colon carcinogenesis in both preclinical models and in humans. He reviewed recent experimental studies suggesting that polyamines may be mechanistically involved in colonic inflammatory processes. Genetic epidemiology results indicate that a single nucleotide polymorphism influencing the expression of a polyamine biosynthetic gene is associated with both, risk of colon polyp occurrence and recurrence, as well as the response to aspirin as a polyp preventive agent. Targeting polyamine synthesis and inflammation can be an effective strategy for preventing the occurrence of the advanced and/or multiple adenomas that are most closely associated with the development of colon cancers in humans. A prospective, randomized, placebo-controlled clinical trial of the combination difluoromethylornithine (DFMO), a selective inhibitor of polyamine synthesis, and sulindac, a

nonsteroidal anti-inflammatory drug, found that the 3-year treatment was associated with a 70% reduction of recurrence of all adenomas, and more than 90% reduction of recurrence of advanced and/or multiple adenomas, without evidence of serious toxicities. Similarly, in men with a family history of prostate cancer, those receiving DFMO in a Phase 2 pilot trial had a smaller increase in prostate volume than those on placebo. DFMO caused a large reduction of prostate putrescine levels compared with an increase in men taking placebo. Stratification by ornithine decarboxylase genotype showed that DFMO reduced prostate volume and putrescine levels in the AA + GA group but not in the GG group. Thus, DFMO induced a decrease of both, prostate putrescine levels and the rate of prostate growth. Dr. Gerner stressed the potential of this compound for either prostate cancer or hyperplasia.

In one of the most provocative sessions of the conference, **Frank Meyskens** from the University of California at Irvine/CA, USA proposed a novel mechanism, whereby heavy metals, particularly cadmium, may interact with UVB light to induce cutaneous melanomas. A large body of epidemiological data indicates that heavy metal exposure is strongly associated with the development of melanoma. Additional studies of patients who have received metal-on-metal hip replacements show a marked increase in cutaneous melanoma. In these patients, chromium and cobalt levels rise more than 10-fold in the 2 years after joint replacement. In published studies of hip replacement patients, relative risks for developing melanoma increased more than 40% with follow-up intervals for 10 or more years after arthroplasty. Chronic exposure to chromium in combination with UV light has been shown to induce skin cancer in a mouse model. When human melanocytes are incubated with hexavalent chromium, the cells become senescent but replicate and form secondary colonies. Clinical data shows aneuploidy in buccal and urinary cells from patients with metal-on-metal hip replacements indicating a possible link between joint replacement and increasing incidence of human melanoma.

### **Session 3: Infection and cancer Prevention: Hepatitis and *H. pylori***

Describing one of the great public health successes in cancer prevention, **Mei-Hwei Chang** of the National University Hospital in Taipei/Taiwan reviewed, how chronic hepatitis B infection causes liver inflammation, injury and regeneration with resulting chronic hepatitis and liver cirrhosis, that can lead to hepatocellular carcinoma. Hepatitis B virus is the most common etiologic agent for primary liver tumors, which are among the five most common cancers in the world. The first universal hepatitis B vaccination program was launched in Taiwan in 1984 and has reduced the prevalence of hepatitis B infection by approximately 90% since the program's inception. Data now show that vaccination also decreases the risk of primary hepatocellular carcinoma with cases occurring only in individuals with incomplete vaccination, those women with prenatal maternal hepatitis B surface antigen positivity, and those with e-antigen positivity. Additional efforts to assure nearly universal vaccination in endemic areas hold the promise to reduce the incidence of primary liver tumors even further.

In a related presentation, **Timothy Morgan** from the Long Beach Veterans Administration System in California/USA reviewed the risk of liver tumors with hepatitis C infection. While there is no vaccine yet to prevent hepatitis C infection, its transmission could be reduced by measures to reduce primary infection, by curative treatment of patients infected with hepatitis C and by chemoprevention among patients in whom their hepatitis C infection cannot be cured. The incidence of HCV-infection has decreased by more than 90% over the past 20 years, and interferon and ribavirin can reduce the risk of primary liver cancer in infected individuals by 70 to 90 percent. Non-antiviral trials are being conducted to determine whether S-adenosylmethionine, protease inhibitors or HCV polymerase inhibitors can prevent primary liver tumors in patients with chronic HBV (or rather HCV?) infection. Both the cost and toxicity of HCV protease or polymerase inhibitors are high, and the search for safe and inexpensive agents is ongoing.

**Javier Torres** of the IMSS Unidad de Investigacion en Enfermedades Infecciosas in Mexico-City/Mexico reviewed the relationship between *H. pylori* infection and gastric cancer in Latin American countries. He noted that *H. pylori* colonizes the gastric mucosa of humans early in life establishing an unusual and long-lasting chronic inflammation of the mucosa. Reactive oxygen and nitrate compounds produced by activated inflammatory cells threaten DNA stability. Risk factors for gastric cancer are multifactorial and include those of the host, the bacteria and environmental factors such as diet or lifestyle habits. All of these factors vary from country to country and within ethnic groups. In Latin America there are countries with very high mortality from gastric cancer such as Chile and Columbia as well as countries with very low rates such as Mexico and Argentina. Differences in *H. pylori* infection rates alone do not explain the differences in mortality from gastric cancer, given that infection rates in most Latin American countries exceed 80% including countries with the lowest rates of gastric cancer mortality. Differences in genes that determine virulence of *H. pylori* may partially explain their carcinogenic potential. *H. pylori* strains from high-risk areas induce higher levels of oxidative and nitroso-reactive compounds from inflammatory cells. Genetic studies in Mexico and Paraguay suggest that polymorphisms in genes that control innate and inflammatory processes may increase the risk of gastric cancer. Among environmental factors, cola drinks and smoking appear to increase risk while eating fruits and vegetables rich in antioxidants offer some primary protection and even regression of early precancerous lesions.

#### **Session 4: Prevention of Prostate Cancer: PSA Screening and Beyond**

**Hans-Peter Schmid** from the Urology Department of the Kantonsspital St. Gallen/Switzerland reviewed the nutritional aspects of primary prostate cancer prevention. Risk factors for prostate cancer include heredity, ethnic origin and increasing age. There are also geographic variations in incidence suggesting, that environment plays a significant role. Nutritional factors that may influence risk of the

disease include total energy intake, dietary fat, cooked meat, micronutrients, calcium, selenium, isoflavonoids, flavonoids, lignans, and vitamins (carotenoids, retinoids, vitamins C, D and E). The selenium and vitamin E SELECT prevention trial is a population-based, prospective randomized clinical trial that was designed to examine the effect of selenium and vitamin E on prostate cancer risk reduction. SELECT participants were asked to stop taking study supplements in the fall of 2008 when a review of the data showed there was no benefit to continue taking vitamin E and/or selenium to prevent prostate cancer. Even though they no longer take study supplements, 31,000 participants remain in the trial. The men enrolled provide a chance to observe changes in their health and risk for prostate cancer. The study is now conducting centralized follow-up during which staff at over 400 SELECT study sites will talk about centralized follow-up with the participants. The SELECT trial demonstrated that vitamin E and/or selenium (at the tested doses) do not prevent prostate cancer in men over 50. More research needs to be done before these and other substances should be endorsed as cancer prevention agents.

**Dipen Parekh** from the University of Texas in San Antonio/USA reviewed the role of 5- $\alpha$ -reductase inhibitors in the chemoprevention of prostate cancer. The Prostate Cancer Prevention Trial (PCPT) compared the ability of the 5 $\alpha$ -reductase inhibitor finasteride (5 mg/day) versus placebo to reduce the risk of prostate cancer. Prostate cancers were detected during the study by biopsies following an abnormal digital rectal examination (DRE) and/or elevated serum prostate-specific antigen (PSA) level or in end-of-study biopsies that were performed regardless of DRE/PSA status. The trial found a 25% reduction in the cumulative number of prostate cancers identified during the 7-year period of follow-up, including those in the end-of-study biopsies, in the finasteride group. The proportion and number of high-grade tumors were higher in the finasteride group than in the placebo group: 37.0% versus 22.2% of the graded tumors in the placebo group. The increased risk of high-grade disease with finasteride in the PCPT was noted in the first year, and the relative risk did not increase over time, raising the suspicion that the increase may have been due to causes other than induced aggressive

disease. This was due, in part, to the improved detection of high-grade lesions due to decreased prostatic volume in the finasteride group. Finasteride is associated with a reduction in the risk of prostate cancer, decreased urinary symptoms, and decreased complications of an enlarged prostate. Side effects include insignificantly reduced sexual function and the expense of the medication.

Professor **Fritz Schröder** from Rotterdam/The Netherlands, the “grand old man” of European Urology, presented a comprehensive review about how to adjust to the totally confused situation of PSA screening of prostate cancer after the recent publication of the two pivotal large secondary prevention trials in Europe and in the USA. While there was no benefit seen at all in the US-trial, some significant, but modest benefit for PSA-Screening in reducing prostate cancer incidence was observed in the (numerically considerably larger and technically not completely comparable) European sister trial, but there remain many open and delicate questions for adequate counseling of risk persons, and it is questionable, whether there will be further such trials in view of their immense costs and logistic problems. More emphasis should therefore be placed on effective primary, pharmacologic prevention of prostate cancer in males at increased risk.

### **Session 5: Hormone Replacement Therapy, Lifestyle and Breast Cancer Prevention**

**Anthony Howell** from the Christie Hospital and Cancer Center in Manchester/UK reviewed the extensive literature related to the relationship between hormone replacement therapy and breast cancer risk. The Women’s Health Initiative in the US enrolled a primary prevention cohort of more than 16,000 women free of coronary disease at the outset. The large sample size provided adequate power for detecting multiple outcomes, and the findings were conclusive: Conjugated equine estrogen plus medroxyprogesterone acetate significantly increased the rates of coronary heart disease, stroke, pulmonary embolism and breast cancer. These risks outweighed the reduced rates of colon cancer and fractures, especially when risk of dementia was also shown to increase among hormone-treated women

at least 65 years old at the start of the trial. Two years later results of a second WHI trial that examined the effects of conjugated equine estrogen alone among nearly 11,000 women with hysterectomy were published. The findings were less adverse with rates of stroke and mild cognitive impairment or dementia increased significantly in the hormone-treated group, while coronary heart disease and breast cancer incidence decreased, although not statistically significantly. It is also known that early oophorectomy increases the risk of heart disease so that hormone replacement may be indicated in younger women. Progestin treatment expands the number of tumor stem cells via a paracrine effect and may explain the differential effect of estrogen versus estrogen plus progestins on breast cancer risk.

**Gad Rennert** from the Department of Community Medicine and Epidemiology and the Carmel Medical Center in Haifa/Israel reviewed the relationship between commonly used medications and the risk of cancer. Nonsteroidal anti-inflammatory drugs, Cox-2 inhibitors, statins, bisphosphonates, hormone replacement therapy, levothyroxine, colchicine, allopurinol, and metformin have all reported varying associations between the agent and the risk of various malignancies. Much of the data arise from observational studies, and few randomized trials have been conducted. The observational data are prone to a variety of biases, and retrospective studies are equally problematic. Differences in study design and among different drugs within a class of drugs can impact results as can duration of use, dosage, route of administration, and differences among ethnically diverse populations. Much detailed, prospective and disease-centered work remains to be done to understand more completely how commonly used medications affect cancer risk.

**Christine Friedenreich** from Alberta Health Services Cancer Care, Calgary, Alberta/Canada reviewed the epidemiologic evidence and biological mechanisms whereby physical activity may affect the risk of breast cancer. Nearly 100 observational epidemiologic studies have been conducted worldwide on the association between exercise and the risk of breast cancer. The reported risk reduction is about 30% when comparing the participants with the highest to lowest activity levels. There is

evidence of a dose-response effect of increasing breast cancer risk reduction with increasing levels of physical activity in these studies. Sustained activity done throughout the lifetime appears to have the most benefit, although activity done in the postmenopausal period has been shown to reduce breast cancer risk even more than activity done before menopause. Both moderate and vigorous activity reduce risk with a somewhat greater benefit associated with vigorous activity. The effect of physical activity is somewhat stronger in normal-weight women, in non-white women, in those with hormone receptor-negative tumors, in women with a family history of breast cancer, and in parous women. The mechanisms whereby exercise reduces breast cancer risk involve effects on circulating sex hormone levels, insulin resistance, inflammation, and body composition. She summarized a two-center, two-arm randomized controlled trial of exercise in 320 postmenopausal, sedentary women age 50 to 74 years who were randomly assigned to a 1-year aerobic exercise intervention of 225 min/wk or to a control group who maintained their usual level of activity. Baseline, 6-month, and 12-month assessments of estrone, estradiol, androstenedione, and testosterone were quantified by radioimmunoassay after extraction, and SHBG was quantified by an immunometric assay. Women in the intervention group exercised an average of 3.6 d/wk for 178 min/wk. At 12 months, statistically significant reductions in estradiol and increases in SHBG were observed in the exercise group compared with the control group. No significant differences in estrone, androstenedione, and testosterone levels were observed between exercisers and controls at 12 months. This trial found, therefore, that previously sedentary postmenopausal women can adhere to a moderate- to vigorous-intensity exercise program that results in changes in estradiol and SHBG concentrations that are consistent with a lower risk for postmenopausal breast cancer.

## Session 6: Chemoprevention of Breast Cancer: the Trial Facts

**Victor Vogel** from the National Surgical Adjuvant Breast and Bowel project (NSABP) in Pittsburgh, PA/USA reported the long-term analysis of the Study of Tamoxifen and Raloxifene (STAR trial) now with a median follow-up of 81 months versus 47 months in the initial report. Women in STAR were postmenopausal,  $\geq 35$  years old, with a modified Gail-model 5-year breast-cancer risk of at least 1.66%. They were randomly assigned to receive either tamoxifen (20 mg/d) or raloxifene (60 mg/d) for 5 years. The risk ratio (RRs; raloxifene:tamoxifen) for invasive breast cancer were 1.24 and 1.22 for noninvasive disease. RRs widened for invasive breast cancer and narrowed for noninvasive disease compared to the initial results. Toxicity with raloxifene was markedly reduced for endometrial cancer; for uterine hyperplasia, and for thromboembolic events. There were no significant mortality differences. Long-term, raloxifene retained 76% of the effectiveness of tamoxifen in preventing invasive disease and grew closer to tamoxifen in preventing noninvasive disease, with far less toxicity (e.g., highly significantly less endometrial cancer). The results should encourage both widespread acceptance of raloxifene and greater acceptance of tamoxifen for breast-cancer risk reduction.

**Trevor Powles** from the Parkside Oncology Clinic in London/UK explored the promise offered by new agents for the antihormonal prevention of breast cancer. Both preclinical and early clinical data indicate that arzoxifene is more potent with greater bioavailability than the second generation selective estrogen receptor modulator raloxifene. A phase 3, multicenter, placebo-controlled, double-blind trial of more than 9000 postmenopausal women with osteoporosis or low bone mineral density, randomly assigned arzoxifene 20mg/d or placebo. The primary endpoints were the incidences of radiographic vertebral fracture in the osteoporotic population and invasive breast cancer in all study participants. The trial demonstrated a 41% reduction in the incidence of vertebral fractures and a 56% percent reduction in incidence of invasive breast cancer. The incidence of invasive breast cancer in the placebo group was

higher in the women who had a Gail score  $>1.66$  compared to  $\leq 1.66$  and in those with low bone mass versus osteoporosis, but the risk reduction with arzoxifene was similar between Gail risk groups and between low bone mass and osteoporosis groups. Other findings included no significant reduction in non-vertebral fractures or cardiovascular events. There was a significant increase in venous thromboembolism, gall bladder disease, pulmonary obstructive/infective disorders, hot flushes, muscle cramps and gynecological-related events in the arzoxifene group.

Lasofoxifene is a nonsteroidal selective estrogen-receptor modulator that decreases bone resorption, bone loss, and low-density- lipoprotein (LDL) cholesterol in postmenopausal women. The PEARL trial was an international, randomized, placebo-controlled trial. Subjects received one gram of calcium and 400 to 800 IU of vitamin D and placebo during a 6- to 8-week run-in period; women who received 75% or more of these pills were randomly assigned to receive lasofoxifene, at a dose of either 0.25 mg per day (the lower-dose lasofoxifene group) or 0.5 mg per day (the higher-dose lasofoxifene group), or placebo. Lasofoxifene at a dose of 0.5 mg per day, as compared with placebo, was associated with reduced risks of vertebral fracture, nonvertebral fracture, ER-positive breast cancer, coronary heart disease events, and stroke. Lasofoxifene at a dose of 0.25 mg per day, as compared with placebo, was associated with reduced risks of vertebral fracture and stroke. Both the lower and higher doses, as compared with placebo, were associated with an increase in venous thromboembolic events. Endometrial cancer risk was not increased. Therefore, in postmenopausal women with osteoporosis, lasofoxifene at a dose of 0.5 mg per day was associated with reduced risks of nonvertebral and vertebral fractures, ER-positive breast cancer, coronary heart disease, and stroke but an increased risk of venous thromboembolic events similar to previously reported selective estrogen receptor modulators. Despite the encouraging results from a number of published trials, the need to treat relatively large numbers of women to prevent a single case of breast cancer still remains. The identification of women with a high probability of developing ER-positive breast cancer has become a research priority.

**John Forbes** from the University of Newcastle, NSW/Australia ...(Abstract not available: Ask John to complete this in “half a page”!)

**Andrea Decensi** from the Department of Oncology at Galliera University Hospital in Genova and the European Institute of Oncology in Milano/both Italy summarized the Italian experience with retinoids and low-dose tamoxifen for chemoprevention of breast cancer. Although the agonistic activity of tamoxifen reduces osteoporotic bone fractures, this property increases the risk of endometrial tumors and venous thromboembolism. The risk of endometrial cancer related to tamoxifen is time and dose dependent. Doses of either 5 or 1 mg/d of tamoxifen have a similar antiproliferative effect on Ki-67 expression compared with the standard dose of 20 mg, and lower doses have fewer effects on circulating biomarkers of tamoxifen estrogenicity, including insulin-like growth factor I (IGF-I), sex hormone binding globulin, low-density lipoprotein cholesterol, and antithrombin III. Retinoids have extensively been studied as preventive agents in breast cancer, and fenretinide administered for 5 years induces a 35% reduction in contralateral breast cancer and ipsilateral reappearance in premenopausal women. Fenretinide administration for 1 year in premenopausal women is associated with a reduction of plasma IGF-I and an increase in IGF-binding protein 3 (IGFBP-3) and predict risk of second breast cancer risk. Mammographic percent density assessed by computerized methods has also been associated with increased breast cancer risk in prospective studies, and reduction of breast density among women under age 45 is associated with reduction in cancer incidence for women taking tamoxifen. Because the combination of tamoxifen and fenretinide is synergistic *in vivo*, Decensi and his colleagues conducted a clinical study in premenopausal women using the change in plasma IGF-I and mammographic density over 2 years as surrogate endpoints. Premenopausal women were randomly assigned in a double-blind four-arm trial to receive tamoxifen 5 mg/d, fenretinide 200 mg/d, both agents, or placebo for 2 years. Patients were included if they had an excised ductal carcinoma *in situ*, lobular carcinoma *in situ*, minimal invasive breast cancer, or a 5-year Gail risk  $\geq 1.3\%$ . After a median follow-up of 40 months,

there was a reduction in IGF-I levels for patients on tamoxifen, fenretinide, tamoxifen plus fenretinide, and placebo. Recruitment was stopped based on the lack of an interaction on IGF-I levels, which was a primary end point for the trial. Baseline IGF-I and mammographic density did not predict breast neoplastic events, nor did change in mammographic density. There was no difference in menopausal symptoms, endometrial thickness, polyps, or ovarian cysts among treatment arms. There were no differences in the incidence of breast cancer among the study arms. The combination of low-dose tamoxifen and fenretinide is safe but not synergistic in lowering IGF-I levels in premenopausal women. A phase III trial of low-dose tamoxifen in women with either ductal or lobular intraepithelial neoplastic lesions has commenced enrolling patients.

**Powell Brown** from the University of Texas M. D. Anderson Cancer Center reviewed novel chemopreventive agents for preventing ER-negative breast cancer that are currently under investigation. These agents modulate non-endocrine biochemical pathways that are involved in regulating the growth of normal and malignant cells independent of ER status. Aberrant expression of COX-2 and prostaglandins has been observed in many cancers including colon and breast cancers, and 40% of human breast cancers show over-expression of COX-2. COX-2 expression, in turn, is correlated with Her-2 protein levels suggesting that over-expression of COX-2 is involved in breast cancer development. Numerous studies have tested the cancer preventive effect of various NSAIDs and selective COX-2 inhibitors, and some selective COX-2 inhibitors significantly reduce the incidence and multiplicity of rat mammary tumors. COX-2 inhibitors carry a potential risk, however, for increased occurrence of thrombotic cardiovascular events including a slight increase in the risk of heart attacks. These rare but serious side effects likely will limit the widespread use of COX-2 inhibitors as cancer prevention agents.

Clinical evidence suggests that over-expression of growth factor receptors in breast cancer, especially those of the EGFR/HER2 family, is associated with resistance to endocrine therapy and, in particular, to tamoxifen. Inhibition of EGFR signaling can overcome resistance to tamoxifen and

fulvestrant and delay the emergence of therapeutic resistance. Activation of certain downstream kinase signaling molecules (such as MAPK and AKT) may also be associated with endocrine resistance, so that targeting these signaling elements or their downstream effectors with agents such as monoclonal antibodies, tyrosine kinase inhibitors, Raf kinase inhibitors, farnesyl transferase inhibitors, and mTOR inhibitors may modulate endocrine response and delay resistance. Ongoing clinical studies are examining whether combining endocrine therapy with a variety of novel targeted therapies may help overcome endocrine resistance and improve treatment outcomes. A more complete blockade of growth factor receptor pathways may be needed to more effectively overcome endocrine resistance. Thus, either multiple signaling inhibitors or agents with multiple kinase targeting capabilities may need to be tested together with antiendocrine therapy.

### **Session 7: International Expert Consensus on Breast Cancer Chemoprevention**

On the basis of the extensive data presented in the preceding session on “trial facts”, this last (and longest) session of the 6<sup>th</sup> international symposium on Clinical Cancer Prevention in St.Gallen was exclusively devoted to an international expert consensus on Breast Cancer Chemoprevention, chaired by **Jack Cuzick** from the Wolfson Institute of Preventive Medicine in London/UK, president of the International Society of Cancer Prevention and by **Florian Otto** from the Tumor- and Breast Center ZeTuP in St.Gallen/Switzerland, the Scientific Secretary General of this meeting. Much time of the panel discussion was devoted to the problems of representative surrogate markers for early breast cancer development and also to the strange fact, that – despite several positive randomized prevention trial outcomes (NSABP-P1 and –P2 as well as IBIS-1) – neither respective women at increased risk nor the medical community have been making adequate use of these preventive possibilities, not even within the USA, where the FDA has licensed Tamoxifen and Raloxifen for chemoprevention of breast cancer years ago. There was general agreement, that the term “chemo”-prevention in itself and also the

psychological attachment of drugs like Tamoxifen to the treatment of advanced metastatic breast cancer might not be very helpful in expanding the use of such compounds among otherwise healthy risk persons for breast cancer, not to speak of the still considerable side-effects of the SERM's and Aromatase Inhibitors, presently used to pharmacologically prevent breast cancer in current prevention trials. A comprehensive review of this consensus session on "Pharmacological Prevention of Breast Cancer" is presently prepared by the panelists and will be published later this year in Lancet Oncology.

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