P16

A Phase II Clinical Trial of Anethole Dithiolethione (Sialor®, Sulfarlem®) in Smokers with Bronchial Dysplasia

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Pre-clinical studies suggested that anethole dithiolethione (ADT) may be an effective chemopreventive agent for lung cancer. This is a Phase IIb study to determine the potential effect of ADT in current and former smokers with premalignant bronchial lesions using bronchial dysplasia as the primary surrogate end-point biomarker (SEB). One hundred current and former smokers with a smoking history of ≥30 pack-years (e.g. 1 pack per day for 30 years or more) with one or more sites of bronchial dysplasia identified by fluorescence bronchoscopy directed bronchial biopsies were treated with ADT at a dose of 25 mg orally TID for six months. At least 4 bronchial biopsies were taken per subject including a minimum of two random biopsies from apparently normal areas. The same areas were re-biopsied after 6 months of study medication. Any new areas suggestive of dysplasia were also biopsied. Changes in the histopathology grade and quantitative nuclear morphometry indices were assessed before and after treatment.

In the site by site analysis, regression of dysplastic lesions to hyperplasia/normal was 53% in the ADT group versus 38% in the placebo group. Appearance of new dysplastic lesion or progression of pre-existing dysplastic lesions was 7% in the ADT group and 18% in the placebo group. The difference in regression and progression between the two groups was statistically significant (P=0.0003). In the person specific analysis, the regression rates were 27% in the ADT group and 11% in the placebo group. The progression rate was lower in the ADT group (32% versus 60%). The difference in regression and progression between the two groups was statistically significant (P=0.031). Adverse events were minor gastrointestinal symptoms that resolved with dose reduction or discontinuation of the medication.

Our results suggest for the first time in humans that anethole dithiolethione (Sialor®, Sulfarlem®) is a potentially efficacious chemoprevention agent for lung cancer; its therapeutic effect is based on its radical scavenger and gluthathione-inducer properties.

Breast Cancer

P17

Human Breast Epithelial Cell (HBEC) Apoptotic Pathway Modulated by Estrogen (E)-Estrogen Receptor (ER)-Activated Genes Phosphorylation

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Breast malignant cells (HBCC) grow unrestrained, promote autonomous growth that does not respond to normal cheeks & balances for cell growth. In long term cultivation the Breast malignant cells ignore normal cell limitations, contact inhibition to stop dividing when they come In contact with each other, and lose the properties of adhesion and cell-to-cell recognition (Hakim, Arch. Geschwultforchung 47:332-350,1979) This study reports on gene expression during conversion of human apithelial cello (HBEC) into breast carcinoma cells (HBCC) (Hakim, Expt. Cell Res. 47:332-350,1979) and its relationship to the genes modulating apoptotic processes contributing to the prevention of the various stages (initiation, prevention & invasion)and killing of the tumor cells with a prescheduled malignant cell death. HBEC & HBCC cells were obtained at resection of benign (2) and post-menopausal primary(S) and metastatic (5) breast tissues. In parallel breast carcinoma: ER+ (MCF-7, TsTd, ZR-75-1) & ER− (MDA-MB-466) BT-20, Hs57BT) cell lines were cultured under well established conditions. cDNA was cloned from HBCC (Hakim, FASEB 2/6, 8719, 1988) was transfected into ER RBCC which contained amplified C-erb-2/Neu & mutated P 53 as described In (Hakim, Naturwissenschaften 74:593,1987, ibid Diagnostics & Clin. Testing 2:30-39,1989; J. Surg. Oncol. 40:21-31, 1989 & Naturwissenschaften 75:361, 1989). The + cello were then injected into BALB/c female nude Nu/Nu mice.

ER+ and ER− HBCC treated directly with anti-protein phosphatase inhibitor blocked tumor cell proliferation both in vivo and in vitro. When examined these cells showed high levels of Bcl-2, P53 and Caspase-3 activity. ER− HBCC and ER+ HBCC treated with estradiol proliferated and developed fatal tumors which contained amplified C-erb-2/Neu & mutated P53. ER− HBCC cells transfected with HEBC. cDNA failed to proliferate in vivo. In-vitro culture produced cells with wild P53, Bcl-2 with moderate Caspase-3 activity, and P21 phosphate turnover. The presence of estradiol in n culture enhanced proliferation of these cells. These findings point to the role of phosphorytion mechanisms on HBCC gene expression, phosphorylation of the wP53 modulates the cell cycle, the Bcl-2 gene modulates Caspase activity and the Apoptotic response and tumor cell viability. Estradiol catalyzes gene expression through thymidine phosphorylase activation.

P18

The Influence of Macro- and Microenvironmental Factors at the Risk of Developing Female Reproductive System Cancer and Breast Cancer in Lodz Region (Centre of Poland)

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In Lodz region we have the big number of disease at the female reproductive system cancer and breast cancer. This region is at the seventh place in respect of woman's risk of dying at the female reproductive system cancer and breast cancer. The studies show the relationship between style of living and the others risk factors and the later development of cancers: age, previous cancer, family history of cancer, menstrual problems, obesity, prolonged use of oral contraceptives or estrogen replacement therapy, diet, alcohol, tobacco, viruses, chemicals and physicals factors and the others.

Conclusion: We have found correlation between style of living (diet, alcohol, tobacco) and oncological risk in relation to breast and cervical cancer. We have not found any correlation between oral contraceptives and cancer risk.

P19

Oncogenic Transformation and Mutation Induced in Human Cell Lines by Mammography X-Rays

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The aim of our study was to measure the neoplastic and mutagenic potential of soft diagnostic mammography X-rays (29 kVp) relative to conventional X-rays (200 kVp) in human cell lines. Neoplastic transformation was assayed using the hybrid cell line (HeLa x skin fibroblast). We found for both X-rays a linear-quadratic relationship between transformation frequency and absorbed dose. At low doses mammography X-rays were 4.3-fbid more efficient than conventional X-rays at inducing neoplastic transformation. The relative biologial efficiency (RBE) of mammography X-rays decreased at higher doses. Our studies on HPRT-mutation induction in SW0-transformed human lung fibroblast showed a similar trend. The mutagenic potential of mammography X-rays at low doses (<0.5 Gy) was 4.2-fold higher compared with conventional X-rays. Familial predisposed women heterozygous for an inherited mutation in a tumour suppressor gene (BRCA1 and BRCA2) are at a higher risk for loss of tumour suppressor gene function than normal women because only one instead of two intact alleles needs to be inactivated by a radiation-induced mutation. Based on the mutation induction of $4.1 \times 10^{-5} \times D/Gy$ measured for the human HPIRT gene (42.83 kb), an average absorbed dose of 3 mGy per mammography and an average breast of 500g with about 10^{11} epithelial target cells, it can be calculated that about 16 000 heterozygous BRCA (+/−) epithelial breast cells will become homozygous (−/−) by a single mammogram.. This number increases to 64 000 BRCA (−/−) deficient cells when taking into account the existence of at least two BRCA genes each with on the average the double size of the HPRT gene. In

contrast, for not-predisposed women 2.7 BRCA (−/−) deficient breast epithelial cells per mammography exposure were calculated. It is not known whether these mammography-induced BIRCA (−/−) deficient breast epithelial cells may translate into breast cancer risk. These findings should, however, stimulate a reevaluation of the risk assessment of mammography for familial predisposed women. In contrast, for not predisposed women the risk for a mutation in each of the tumour suppressor alleles by mammography is much lower. Our results contradict the ICRP Publication 60 which attributes the same biological efficiencies to conventional and mammography X-rays.

P20

Intensified Surveillance for Women at High Risk for Breast Cancer

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Prophylactic mastectomy has been shown to reduce the risk of breast cancer by more than 90% in high risk women. But as it is a very invasive and mutilating procedure, only a minority of the high risk women in Germany opt for this surgical intervention.

Goals: The purpose of this study is to review the intensive surveillance program that is offered as another management option to women at high risk for breast and ovarian cancer, who have been counseled in our hereditary cancer clinic.

Methods: Besides semiannual clinical breast and pelvic exams the program comprises annual mammograms, annual breast-MRIs, semiannual breast ultrasounds and transvaginal ultrasounds in combination with CA-125 level measurements. Since the beginning of this program in June 1999, 69 women are participating. 20% are carriers of a *BRCA1/2*-mutation, 14% are carrying a mutation of uncertain significance and 49% were tested negative. For 17% the gene-analysis is not finished yet. The average age is 42 yrs (26 ± 58 yrs.).

Results: So far one new breast cancer and one local recurrency were detected among the participants. The newly diagnosed breast cancer (stage IIA) could be seen on mammography, MRI and ultrasound, the local recurrency was detected by MRI. Both patients were BRCA1/2 negative. Ovarian abnormalities have not been found among the participants.

Conclusions: Intensified surveillance seems to be a highly acceptable alternative to prophylactic surgery for mutation-carriers as well as for women with a strong family history but a negative test-result. Taken the cost-effectiveness into account, the role of regular breast-MRIs as part of the intensive screening program remains to be investigated.

P21

Position on Prevention of Breast Cancer – An Investigation of 2100 Women

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Problem: Promising though contradictory results (Fisher, Veronesi, Powles) so far have been obtained from studies into prevention of breast cancer. More studies, consequently, are being initiated (STARTrial). Only few and regionally limited projects have been run in Germany (Beckmann et al, Paepke et al). Knowledge about the possibility and acceptance of preventive medication in the target group is considered to be the prerequisite for a nationwide prevention study as planned by the German Chemoprevention Group (DACH).

Material and Methods: A 47-item questionnaire was set up and was laid out in gynaecological outpatient units to probe for general knowledge of breast cancer and risk factors. 2600 copies of questionnaires were distributed, and 2110 were evaluated (feedback rate: 81.5%).

Results: 57.5% of all interviewees would be ready to change their lifestyle for risk reduction, while 5.9% were not, and 34.7% would not male up their mind.

Table: Attitudes to prevention

	Reduction of breast cancer risk by use medication		Willingness to use preventive medication	
	Possible (%)	impossible (%)	Yes (%)	No (%)
Total	20.9	79.1	53.7	46.3

Conclusion: The high feedback rate reflects the great interest taken by the female population in the issue of breast cancer. There is a general demand for more information. Knowledge is inadequate regarding possible prevention of breast cancer medication. The conclusion may be drawn for the female population in the two regions covered that, on principle, chemical prevention is generally accepted. Hence, a German-wide study appears to be feasible.

P22

Perceptions of Risk and Motivations for Counselling in Portuguese Women from Families at High Risk of Breast Cancer

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Portuguese women from families at high risk of breast cancer have been traditionally offered early radiological diagnostic screening and rarely (usually if women insist) prophylactic surgery. We implemented counseling for these women in a multidisciplinary context and in this analysis we study the motivations of women to look for counseling and their perceptions of risk.

From December/00 to September/01, 52 families were registered and all individuals (1-3 per family) received a baseline questionnaire with questions concerning their worries and attitudes towards self-perceived risk. Counseling was offered based on predictive analysis, using the Gail, Claus and BR-CAPRO models. All women had at least one relative with cancer: 45 (87%) breast cancer, 4 (8%) ovarian cancer and 3 (5%) other cancers. 54 (75%) were healthy and 18 (25%) were cancer survivors, mostly from breast cancer 16 (89%). For cancer survivors, the main questions were cancer risk in their children (90%) and contralateral prophylactic mastectomy and/or oophorectomy (50%). 35(65%) healthy women considered themselves at high risk from breast cancer; from these 31(89%) had a strong worry about cancer and 5 (14%) had taken life decisions (marriage, children) due to their perceptions of risk. 20(57%) did self-breast examination regurlaly. We are still in the process of pedigree confirmation in 21 families. From the other 31, probable risk of hereditary breast ovarian cancer is low (<10% probability) in 10 families, medium risk (10-25% probability) in 9 and high (>25% probability) in 12. While women from medium and high-risk families had a reasonable perception of their risk this was greatly overestimated by women from low risk families. In conclusion counseling must be tailored according to different needs of these women. Besides considering screening and prophylactic attitudes based on predictive analysis we are now offering BRCA/2 mutation screening in high risk cases and a study to analyze efficacy of counseling is being implemented.

P23

Factors Influencing the Acceptance of Breast Cancer (BC) Screening and Prevention Among the German Female Population

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An important prerequisite for the successful implementation of screening and prevention measures for early BC detection is the knowledge on factors influencing the readiness of women for participation.

The German Working Group on Chemoprevention (DACH) conducted a survey by telephone on 758 women representing an adequate sample of the German female population. In a questionnaire we assessed the participation on screening programmes, the attitudes towards BC prevention and special psychosocial traits such as problem-coverage, behaviour-certitude, self-esteem, contact ability, health, personal body-care, body-contact, sexuality, self-acceptance, acceptance by others, breast-acceptance, breast-problems, general fear, fear of disease, fear of BC ("Frankfurter Selbstkonzeptskalen" FSKN and "Körperkonzeptskalen" FKKS following I.M. Deusinger). Correlations between the questions regarding knowledge about BC, breast examinations and the attitude towards primary or secondary prevention and the psychosocial traits were analysed by a chi-square-test.

83% of the women believe that the chances of a cure of BC are rather bad to none, but 86% believe that early detection can recognise BC in an early and curable stage. 69% of the women quoted to have yearly mammograms. Women with a high fear of BC and a high index on personal body-care were especially

active in regular BC-screening (p < 0.001 and p=0.001 resp.) The main reasons stated not to go to serial breast mammograms was forgetfulness (19%) and fear of the examination (13%). 61% women are willing (23% probably, 14% not) to change their lifestyle if this could reduce their BC-risk. Personal body-care and breast acceptance have a positive influence on the readiness to change lifestyle (p < 0.001 and p=0.005 resp.).

Only 18% of the women believe that medication can reduce the BC-risk, however 43% would use some kind of chemo-prevention if it would reduce their BC-risk. This readiness is positively influenced by the subjects fear of BC and personal body-care (both p < 0.001). Other psychosocial traits showed no significant correlation to the attitudes.

Both, fear of BC and a high index on personal body-care are positively related to the readiness of regular breast examinations, changing lifestyle and usage of chemoprevention and may be used for implementation of screening and prevention programs.

P24

A New Approach for Discovering of Minimal Residual Disease in Patients With Operable Breast Cancer

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The striving of surgeon for achieving better long-term results of surgical treatment of patients with breast cancer put the searching of new Independent prognostic factors for the exit of the treatment. This has become possible in the last decade of XX century when new diagnostic methods as immunochistochemistry, polimerase chain reaction (PCR), cytomorphology etc. entered the clinical practice.

With bone marrow biopsy in patients with breast cancer earlier diagnosis of minimal residual disease is achieved, the approach to those patients is changed and a possibility for discovering women at higher risk is given.

By immunochistochemicaly method in the diagnostics of minimal residual disease in patients with breast cancer, more precise staging Is achieved. This will change the therapeutic approach to these patients.

P25

Pilot Feasibility Study of the Spirotome for Large Core Biopsies in Human Breast Cancer

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Image guided large core biopsy of a suspicious breast lesion addresses optimally the increasing need to obtain samples, big enough to make morphological and molecular biology diagnostic techniques possible in a reliable manner. Also the demand to identify intermediary markers will increase for preventive purposes. At the same time, repeatable medical imaging and patient compliance to screening programs need to avoid unnecessary tissue injury. Finally, the costs of the procedure should be as low as possible to obtain a large diffusion of the technology for the population. For these reasons, large core biopsy systems are now being developed that harvest representative specimen at low costs that cause minimal disruption of the breast parenchyma.

One such system is the Spirotome that is radically different from other soft tissue biopsy devices because the underlying principle is based on a rotational cutting action of the needle on a helix. The system has 4 main parts: the localisation needle, the helical tissue receiving part, the cutting canula and a releasing device. Preclinical experiments showed high performance of the method and optimal tissue specimen. This system was now tested 'in vivo' prior to large-scale clinical trials. Eight female patients with suspicious breast lesions were invited to the program prior to open biopsy or surgery. The lesion had to be 1 cm or more in diameter. After local anaesthesia the lesion was biopsied either under clinical (palpable) or ultrasound (non-palpable) guidance. The harvested specimen was on average 1,8 cm in length and 2,8 mm in diameter. The pathological features were almost identical to open biopsy or surgery since no crush artefacts were noted in the specimen. None of the patients had major discomfort or side effects. No complications were seen and cosmetic results were excellent after one week. The procedure could be entirely followed and guided by ultrasound by the same manipulator. The ultrasound image proved the representativity of the sample during the cutting procedure.

In conclusion, the Spirotome large core biopsy system performs well in the clinical context without longlasting injury to the breast parenchyma or artefacts to the harvested tissue specimen. These results suggest that the Spirotome meets all the criteria that are set forward to address the increasing demands of large core biopsy systems. The system is ready to enter large-scale clinical trials.

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Vascular Endothelial Cell Growth Factor (VEGF) in Comparison With Tissue Polypeptide Antigen (TPA), Cancer Antigen 15-3 (CA 15-3) and Carcinoembryonic Antigen (CEA) in the Follow-Up of Breast Cancer

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Vascular endothelial cell growth factor (VEGF), tissue polypeptide antigen (TPA), cancer antigen 15-3 (CA 15-3) and carcinoembryonic antigen (CEA) were measured in 314 sera of breast cancer patients and in 58 sera of woman without breast cancer. VEGF was determined using a sandwich enzyme immunoassay technique (ELISA) and the tumour markers TPA, CA 15-3 and CEA with an immunoluminometric assay (ILMA). The breast cancer patients were staged according to the TNM classification stages 0-IV (by UICC) in patient groups with a compartible prognosis. Median and range of each stage were investigated. The cut-off values (95th and 97.5th percentile of control group) of VEGF, TPA, CA 15-3

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

P27

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

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

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

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

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

GI-Cancer

P28

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

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

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