PAE treatment significantly lowered the number of adenomas in the small intestine by 38% and 40% (avg ± standard error of the mean (SE) control: 64.7. ± 7.2 vs. CAJ: 40.3 ± 5.0, P = 0.011, and PAE: 38.9 ± 2.9, P = 0.007), whereas tumor numbers in the colon were not affected (avg ± SE control: 1.3 ± 0.3, CAJ: 1.8 ± 0.4, PAE: 0.9 ± 0.2). Adenomas were stronger decreased in the middle and the distal part of the SI than in the proximal part. Further, particularly numbers of medium and large adenomas were significantly reduced by both interventions compared to control. Intestinal cell proliferation, determined by immuno-histochemical staining of proliferating cell nuclear antigen, was not influenced by either intervention. Hematocrit values as an indication of intestinal bleeding were negatively correlated with total tumor numbers in both intervention groups (r = -0.82), whereas a positive correlation was observed between spleen weights and adenoma numbers (r = 0.91). Both parameters were slightly ameliorated by the treatments, with significant effects observed with PAE intervention. Overall, our study suggests that CAJ and PAE should be further investigated as part of a prevention strategy for hereditary and sporadic colorectal cancer.

P35

Cancer chemopreventive and anti-angiogenic activities of xanthohumol from hop (Humulus lupulus L.)

C. Gerhauser[1], R. Hussong[1], E. Bertl[1], K. Klimo[1], N. Frank[1], H. Bartsch[1], H. Becker[2]. [1]*German Cancer Research Center, Toxicology and Cancer Risk Factors, Heidelberg, Germany;* [2]*University of Saarland, Pharmacognosy and Analytical Phytochemistry, Saarbruecken, Germany*

Hop (Humulus lupulus L.) is a good source of phenolic constituents in beer. We investigated a hop extract in a series of test systems indicative of cancer chemopreventive potential and isolated the chalcone xanthohumol (XN) as a most interesting lead structures with high chemopreventive potential at the initiation, promotion and progression stage of carcinogenesis. Although hop is commonly linked with phytoestrogenic effects, we identified XN as a pure estrogen antagonist. Interestingly, XN also affected the generation of estrogens by inhibition of the enzymatic activity of aromatase, which converts testosterone into estrogen. In an uterotrophy assay with prepubertal rats, XN treatment (100 mg/kg bw/day) lowered unstimulated as well as ethinylestradiol-induced uterine weights by about 30%. XN did not cause any adverse effect on female reproduction and on the development of offspring when given either for four weeks prior to or during mating, gestation and nursing. Treatment of male rats prior to mating however significantly (p = 0.027) increased the sex ratio of male to female offspring. Inhibition of angiogenesis represents an innovative approach to cancer chemoprevention. We investigated the angiostatic potential of XN in a human in vitro anti-angiogenic assay premised on the principle of wound healing. We observed dose-dependent reduction of newly formed capillary growth in a concentration range of 0.5 to 10μM. Further mechanistic investigations were performed with HMEC-1, an immortalized human microvascular endothelial cell line. XN effectively inhibited migration of HMEC-1 cells after wounding in a wound closure assay (half-maximal inhibitory concentration IC50=0.03μM). Also, XN effectively inhibited tube-formation on basement membrane matrix at 1, 5 and 10μM, respectively, whereas at 0.1μM, some tubes started to form within the incubation period of 6 h. These effects were only partly due to inhibition of HMEC-1 proliferation, as XN inhibited cell growth with an IC50 of 6.4μM. Xanthohumol also inhibited the transcription of hypoxia-inducible genes under hypoxic conditions. Subcutaneous application of XN (1mg/g body weight) for 14 days to SCID mice bearing human MX-1 breast tumor xenografts significantly reduced the tumor size in treated animals by 82%. Concomitantly, we observed a 30% reduction of tumor-induced neovascularization.

Based on these results, chemopreventive and therapeutic activities of XN will be further investigated.

P36

HMG CoA reductase inhibitors decrease the risk of pancreatic cancer in US veterans: longer use translated to higher protection

V. Khurana[1], G. Caldito[2], J.S. Barkin[3]. [1]*Overton Brooks VA Medical Center, Gastroenterology, Shreveport, LA, United States of America;* [2]*Lousiana State University HSC, Biometry, Shreveport, LA, United States of America;* [3]*Mt. Sinai Medical Center / University of Miami, Gastroenterology, Miami Beach, FL, United States of America*

Background: HMG CoA reductase inhibitors (Statins) are commonly used cholesterol-lowering agents that are noted to suppress tumor growth in cell cultures and several animal models. The anti-tumor effects of statins are exerted by its antiproliferative, proapoptotic, anti-invasive and radio sensitizing properties. Statins induced apoptosis is predominantly mediated through depletion of geranylgeranylated proteins. Anti invasive effects are mediated by RhoA inactivation.

Methods: US Veterans Health Administration (VHA) is organized into 21 administrative regions called Veterans Integrated Service Networks (VISN). VISN 16 or the South Central (US) VA Health Care Network provides health care treatment to >1.4 million veterans in an eight state region. The network, an integrated health care system, includes ten medical centers, 33 community-based outpatient clinics, seven nursing homes, and two domiciliary. The data was queried from Oct 1998 to June 2004, using a retrospective case control design. Statistical analysis was performed using SAS software version 9.0 (Chicago, IL). Multiple logistic regression analysis was used with calculation of odds ratios and 95% confidence intervals. The data was adjusted for age, race, gender, BMI, smoking, alcohol use and diabetes. Patients were placed in the Statin user group if they were using statin prior to the diagnosis of pancreatic cancer.

Results: Of the 483,733 patients in the study, 163,662 (33.8%) were on statins and 475 (0.1%) patients had a primary diagnosis of pancreatic cancer. Statin use of more than 6 months was associated with a risk reduction of pancreatic cancer of 67% (adjusted OR, 0.33; 95% CI, 0.26 to 0.41; p value <0.01). A dose response relationship was noted between statin use duration and pancreatic cancer with 80% risk reduction (adjusted OR, 0.20; 95% CI, 0.33 to 0.71; p value, <0.01) with use of statin for more than 4 years. Furthermore, the protective effect of statin was seen across different age and racial groups, and was irrespective of the presence of diabetes or alcohol use. The protective benefit was not seen in smokers.