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**Linking Underserved Populations with Phytochemical-Rich Diets. A Menu for Program Design and Implementation. C. Engelking.** Arlin Cancer Institute, Westchester Medical Center, Valhalla, NY.

Underserved populations, including African-Americans, Hispanics and the elderly, experience higher prevalence rates for selected cancers; for a variety of reasons, they present later to receive medical attention and have higher overall cancer mortality rates. Although scientific data on nutritional literacy and lifestyle practices related to food selection, preparation and consumption as well as exercise in these populations are limited, it is thought that diet may explain some of the variation in cancer prevalence rates across race and ethnic groups. Studies of migrant populations suggest that environmental causes, such as diet, may be important determinants of cancer risk. It is also recognized that these underserved populations generally consume diets that do not comply with current nutritional recommendations for cancer prevention. For example, findings of the National Health and Nutrition Examination Survey epidemiologic follow-up study revealed that African-Americans have a significantly lower Healthy Eating Index score for consumption of fruits and vegetables, folate and total dietary fiber, all nutrients thought to be associated with lower cancer risk. Reaching these groups with healthy eating messages that result in sustainable behavioral change is challenging and requires a working knowledge of the unique characteristics of the group targeted for intervention. These characteristics include ethnic and cultural attributes, behavior-shaping experiences, values, attitudes and belief systems. Strategies for linking these populations with diets rich in cancer-preventing phytochemicals remain challenging but can be achieved. Such strategies encompass the use of partnership and coalition models (e.g., establishment of nutrition action teams and neighborhood networks), group-targeting using marketing applications (e.g., translation of national guidelines to group vernacular, use of churches and schools as vehicles), individual customization techniques (e.g., personalized print materials, audiovisual and computer messages), mobilization of social support and use of lay health advisors. Programs with demonstrated success should be highlighted to serve as models for action.

**Late Effects in Survivors of Childhood Cancer. Opportunities for Intervention. C. A. Sklar.** Department of Pediatrics, Memorial Sloan Kettering, New York.

Survival rates for children and adolescents diagnosed with cancer have improved dramatically over the past 30 years. Currently, the overall 5-y survival rate for childhood cancer is in excess of 70%. It is estimated that 1 of every 900 young adults is a childhood cancer survivor and that >250,000 childhood cancer survivors are currently residing in the

United States. These impressive survival rates are due, primarily, to improvements in cancer treatments. Contemporary therapy for childhood cancers generally includes the use of multimodality regimens (e.g., the combination of radiation and chemotherapy) and multiagent, highly intensive chemotherapy. Unfortunately, the long-term consequences of such exposures are considerable. Approximately two thirds of childhood cancer survivors will develop some type of medical complication or disability as a direct result of their earlier cancer therapy. We will focus on the late complications that may be amenable to nutritional interventions. These include second cancers, obesity, osteoporosis, premature coronary artery disease and hyperlipidemia.

**Carcinogens in Cooked Meats and Human Cancer. R. Sinha.** Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD.

Diets containing substantial amounts of red meat may increase the risk of colorectal, pancreatic, breast, prostate and renal cancer. The association with red meat intake may be due to a combination of factors, such as content of fat, protein and iron and preparation methods (e.g., cooking, preserving). Laboratory results have shown that meats cooked at high temperatures contain heterocyclic amines (HCA) and polycyclic aromatic hydrocarbons (PAH), which are mutagenic and carcinogenic in animals. Many older epidemiologic studies of colon cancer using surrogates for HCA exposure from meat (e.g., doneness level, surface browning, frying, intake of gravy) produced suggestive but inconsistent results. These discrepancies may have resulted in part from having used dietary questionnaires that combined meat-cooking practices in ways that made the intake of HCA and PAH difficult to estimate. Thus, over the past decade we have taken a multidisciplinary approach to investigating whether the association with red meat intake can be explained by meat-cooking practices that produce mutagens and carcinogens. To estimate intake, two separate databases for HCA and PAH have been developed and used in conjunction with a validated meat-cooking food-frequency questionnaire (FFQ). To develop biological markers of internal exposure, a metabolic study was conducted in which subjects consumed controlled amounts of meat cooked at low and high temperatures. The roles of meat type, cooking methods, doneness levels and meat-cooking mutagens were examined in case-control studies of colorectal adenomas, lung cancers and breast cancers using both questionnaire information and biomarkers. In a case-control study of colorectal adenomas, an increased risk was associated with a high intake of red meat. Most of this risk was due to intake of red meat cooked until well or very well done or to high temperature cooking techniques such as grilling. Linking the FFQ information to the mutagen and carcinogen database enabled us to evaluate the effect on risk of mutagenic activity as well as exposure to several HCA and to 3,4-benzpyrene. An increased risk was associated with higher levels of meat-derived mutagenic activity, intake of 2-amino-3,8-dimethylimidazol[4,5-*f*]quinoxaline (MeIQx), possibly 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) and 3,4-benzpyrene. Even though the results from these case-control studies lend support to a causative role for HCA in human cancer, other larger studies do not. Components of red meat, other than HCA, such as heme iron, fat, nitrite and nitrosamine and salt, must be explored further. This presentation examined the

current epidemiologic knowledge in relation to meat cooking mutagens and evaluated the types of studies that may be required in the future to clarify the association of HCA in human cancers.

**Chemoprevention of Colitis-Associated Colorectal Cancer.** M. L. Clapper, H. S. Cooper, R. Coudry, M. A. Gary and W.-C.L. Chang. Division of Population Science, Fox Chase Cancer Center, Philadelphia, PA.

The increased risk for colorectal malignancies in patients with inflammatory bowel disease, specifically ulcerative colitis, has been well established and increases with age at onset and extent and duration of disease. The cumulative risk of developing colorectal cancer in patients with long-standing pancolitis can reach as high as 33% after 2–3 decades of disease. Both the longevity of inflammatory bowel disease and the development of colitis-associated neoplasms through a dysplasia sequence provide a window of opportunity for chemopreventive intervention. Preclinical experimentation is underway to develop the first therapeutic regimen for the prevention of colitis-associated colorectal dysplasias and cancers using the dextran sulfate sodium (DSS) mouse model.

A detailed characterization of the pathology of DSS-induced colitis suggests that this is a reliable and relevant model for the future development of strategies for the chemoprevention of human colitis-associated colon cancer. In this model, acute (1 cycle) or chronic (2–4 cycles) inflammation is produced by administering DSS to Swiss Webster mice. Each cycle consists of 7 d of 4% DSS followed by 14 d of untreated water. By the end of the fourth cycle, ~20% of the mice develop colonic dysplasias, cancers or both. Similar to humans with ulcerative colitis, DSS-treated mice experience periods of clinical activity and inactivity, possess various degrees of inflammation many months after DSS exposure and develop both flat and polypoid dysplasias and/or cancers that are morphologically identical to those of humans.

The ability of select chemopreventive agents to inhibit colitis-associated colorectal dysplasia and cancer is being evaluated in the DSS mouse model. Although 22% of the mice receiving 4 cycles of DSS developed colorectal neoplasms, the total number of colonic dysplasias and cancers was reduced significantly ( $P = 0.02$ ) in mice receiving the prototypic chemopreventive agent and Phase II enzyme inducer, oltipraz. Furthermore, colorectal cancers were completely eliminated after oltipraz exposure. Oltipraz (250 mg/kg diet) was administered from 2 wk before DSS and throughout the experiment. Consistent with our data from a previous clinical trial, a higher dosage of oltipraz (500 mg/kg diet) was ineffective in reducing colon tumor incidence. The mechanism by which oltipraz inhibits colitis-associated colorectal cancer remains to be determined. Other chemopreventive agents under evaluation by this group include the bile acid, ursodeoxycholic acid, the nonsteroidal anti-inflammatory agent, celecoxib, and the antiproliferative agent, difluoromethylornithine. The primary endpoints of these *in vivo* investigations include the incidence and multiplicity of colonic dysplasias and cancers.

Unique knockout mouse strains have been developed by this group and represent a novel resource for assessing the contribution of genetic background to susceptibility for colitis-associated colorectal cancer. The role of the adenomatous polyposis coli (APC) gene in the development of colitis-associated

neoplasms has been examined. Administration of DSS to a newly derived strain of multiple intestinal neoplasia (*Min*) mice carrying a germline mutation in this gene produced a 15-fold increase in the multiplicity of colonic adenomas, compared with age-matched untreated *Min* mice. A similar analysis of additional colon cancer genes is in progress. Data obtained from these genetically defined mouse strains, when combined with the results of the chemopreventive analyses, are anticipated to facilitate the development of an efficacious regimen for the prevention of colorectal cancer in patients with ulcerative colitis. [Supported by the Cancer Research Foundation of America and by National Institutes of Health NO1 CN05121.]

**Use of Fecal Water as a Biomarker in Dietary Intervention Studies.** G. Rechkemmer, K. Schnaebeler, A. Bub, S. Barth and K. Briviba. Institute of Nutritional Physiology, Federal Research Center for Nutrition, Karlsruhe, Germany.

In epidemiologic studies investigating associations between nutritional factors and cancer, the observed study end point generally is the clinical diagnosis of tumor occurrence. In experimental studies, however, it is desirable to develop biomarkers linked to the early stages of carcinogenesis. In particular, such efforts have been made in colonic carcinogenesis in which the molecular details of the different stages are well characterized. The types of biomarkers necessary in dietary intervention studies are biomarkers of exposure, effect and susceptibility. The rapid advancement of genetic testing, determination of genetic polymorphisms and link of genetic disposition to dietary effects on carcinogenesis is of great scientific interest and importance. Biomarkers of exposure are usually measured in blood plasma, and dose-dependent changes in plasma concentration are studied to evaluate the bioavailability of dietary components. However, in colonic carcinogenesis, it is also important to determine the exposure biomarkers directly in the intestinal lumen or feces and the exposed epithelial cells. In dietary intervention studies with healthy volunteers, the effects of consuming carotenoid-containing foods (carrot and tomato juice) on the carotenoid concentration in fecal water was investigated. Carotenoid concentrations up to 50–60  $\mu\text{mol/L}$  were measured. These values are at least 10 times higher than the maximal concentrations that would be achieved in the plasma after prolonged consumption of carotenoid-rich foods with high bioavailability or using dietary supplements. Investigating the biological effects of carotenoids at concentrations present in fecal water on human colon carcinoma cell lines (HT29) revealed that the high concentrations induced apoptosis in growing cells (50% inhibitory concentration: ~15  $\mu\text{mol/L}$  for  $\beta$ -carotene). Fecal water itself not only induces apoptosis but also markedly reduces the proliferation of colon carcinoma cells. Fecal water (diluted 1:100) caused an inhibition of cell growth by ~50%, indicating a pronounced antiproliferative potential. Intervention with carotenoid-rich foods did not significantly alter the antiproliferative effect of fecal water. In summary, the development and validation of suitable biomarkers is of great importance in dietary intervention studies investigating the link between dietary factors and various molecular and cellular processes of carcinogenesis.

**Diet and Cancer in a Country in Transition. The Case of Uruguay.** P. Boffetta and E. De Stefani.\* International Agency for Research on Cancer, Lyon, France and \*National Cancer Registry, Montevideo, Uruguay.