Abstract

The Eighth Annual Frontiers in Cancer Prevention Research meeting was held in Houston, Texas, in November 2009. This report highlights significant presentations that advance the fields of chemoprevention, clinical trial recruitment and retention, cancer screening including optical imaging, energy balance, and nutritional epidemiology, and health communications and decision making. In findings from the randomized Reduction by Dutasteride of Prostate Cancer Events trial, dutasteride reduced the risk of biopsy-detectable prostate cancer in high-risk men by 23% compared with placebo. Important clues about the dosing and window of susceptibility for supplementation with choline, vitamin D, and folate were revealed from epigenetic research that has implications for future nutritional epidemiology research. Noninvasive optical imaging techniques using endoscopic ultrasound and autofluorescence for the early detection of cancers in the lung, pancreas, and oral cavity are being studied. The report also addresses the challenges of promoting cancer prevention. Understanding how individuals process risk information and make sustained behavior changes and the effect of socioeconomic status on health disparities were identified as critical areas of research. This multidisciplinary research meeting of basic, clinical, and behavioral scientists and epidemiologists continues to play a major role in identifying the research priority areas of cancer prevention, elucidating new mechanisms of carcinogenesis for targeted chemoprevention therapies and delivering a comprehensive strategy for engaging individuals in the unifying goal to reduce cancer incidence. Cancer Prev Res; 3(8); 1044–8. ©2010 AACR.

Chemoprevention Agent Development: Accelerating the Pace

Cancer chemoprevention remains a promising strategy for averting, reversing, and/or suppressing carcinogenesis. However, realizing the true potential of candidate compounds can be time-, labor-, and resource-intensive. Innovative solutions are urgently needed to overcome existing barriers and accelerate the pace of chemoprevention agent development. In this educational session, an array of methodologic, scientific, economic, and regulatory issues were reviewed by an interdisciplinary panel of experts.

The "phase 0" clinical trial design was recently introduced in response to the Food and Drug Administration Critical Path Report (available at http://www.fda.gov). Under this paradigm, first-in-human trials can be initiated more quickly because the required preclinical data are more limited. Phase 0 trials can be used to evaluate pharmacodynamic or pharmacokinetic parameters, using subtherapeutic doses of the investigational agent. Dr. Paul Limburg emphasized that phase 0 trials are most appropriate for investigational agents with (a) a wide therapeutic index, (b) an established mechanism of action, and (c) well-defined biospecimen collection, handling, and processing protocols. With respect to chemoprevention, Dr. Limburg suggested that phase 0 trials might be particularly useful for assessing new compounds that are extracted (or derived) from natural products or existing drugs that have been reformulated to improve delivery or reduce toxicity. Agents that target molecular pathways that could be modulated in premalignant conditions (i.e., Barrett's esophagus) would also be of considerable interest. Because the published experience with phase 0 trials is currently limited, the full utility of this paradigm will become more clearly defined over time.

The challenges associated with making "go/no-go" decisions concerning candidate chemoprevention agents based on observational, experimental, and early-phase clinical trial data were discussed. Using the recently completed Selenium and Vitamin E Cancer Prevention Trial (SELECT) as an illustrative example, Dr. Scott Lippman highlighted the need for strong, consistent, supporting data before embarking on large, lengthy, and costly phase
III trials. Dr. Lippman noted that, in general, selective and nonselective cyclooxygenase-2 inhibitors have shown compelling efficacy in numerous types of studies, but later exhibited widely unanticipated cardiovascular toxicity when subjected to chronic administration in colorectal cancer chemoprevention trials. In contrast, agents such as difluoromethylornithine, of which the molecular target and associated toxicity profile were relatively well established in the chemotherapy setting, could be evaluated for chemopreventive applications with greater efficiency. Moving forward, Dr. Lippman proposed that the “fully stepped” approach to chemoprevention agent development would involve preclinical models, epidemiologic investigation, pharmacogenomic analyses, risk modeling, and early-phase clinical trial evaluation before the initiation of definitive registration trials.

Dr. Jeffrey Moe addressed the regulatory concerns and legal issues pertaining to pharmaceutical interest in chemoprevention agent development. If sufficient patent protection remains to realistically anticipate the recovery of additional research and development costs, new anticancer drugs may be moved “upstream” for potential application in a prevention setting. Given the current limitations on market exclusivity, many pharmaceutical and/or biotechnology companies may not perceive adequate financial opportunity to pursue chemoprevention indications, even when the scientific data seem promising. Dr. Moe discussed several possible solutions that could be considered, including extension of the Orphan Drug Act, prolongation of nonpatent market exclusivity, creation of a “priority review voucher,” and other ideas that may serve to generate increased industry engagement in this high-priority area.

Recruitment/Retention and Clinical Trials

The work being conducted by Dr. Diane Simmons and colleagues at the Center for Information and Study on Clinical Research underscores the importance of engaging the public in clinical research outside of recruitment for a specific study. According to this group’s research, the majority of individuals in the general public are suspicious of clinical research and many do not know where to obtain information on how to participate in studies. To address this barrier to clinical trial participation, Dr. Simmons recommended that investigators take steps to create an atmosphere of trust in clinical research among the general public through campaigns that focus on increasing awareness and knowledge about studies. This approach is consistent with a recent review which found that lack of awareness about studies was an important barrier to minority participation in cancer clinical trials. If individuals are not aware about the availability of studies and subsequently do not have an opportunity to participate, then enrollment is an unrealistic outcome.

Approaches that can be used to increase participation in clinical research among minorities include recruiting through the media and mailings, increasing transportation resources, and having after-hours clinical support. Although these approaches have had some success when implemented in large-scale trials, they have failed in several other studies, according to Dr. Willo Pequegnat from the National Institute of Mental Health. It may be time to move beyond developing recruitment strategies that are based on our intuitive knowledge about barriers to minority participation (e.g., distrust) or focusing only on one factor that is likely to reduce participation (e.g., lack of awareness) and conceptualize study enrollment as a behavioral decision that people make just as they would any other choice about their health. In this way, we would apply constructs from health behavior theory to identify factors that act as barriers and facilitators to participation and use this information to develop evidence-based approaches to enhance minority participation and increase the racial and ethnic diversity of individuals who are recruited to participate in cancer prevention research.

Prostate Cancer: Controversies in Screening and Prevention

Despite the decline in prostate cancer incidence and mortality, the disease continues to present a significant health threat to men as they age. According to the National Cancer Institute estimates, approximately 192,000 men in the United States were diagnosed with prostate cancer in 2009 and more than 27,000 died of the disease in the same year.

The session opened with a discussion by Dr. Ruth Etzioni on the utilization and benefit of prostate-specific antigen (PSA) screening. She noted that before the development of the PSA test, more than 75% of the cases of prostate cancer had not been detected. After the introduction of the test in the late 1980s, there was an initial spike in the incidence of prostate cancer from 400 per 100,000 men-years to a peak of 800 per 100,000 men-years in the early 1990s. New screening tests typically lead to a spike in reported incidence followed by stabilization as the screening method stabilizes. Screening can cause a corollary issue, one of overdiagnosis in which the disease would not have been diagnosed in the absence of screening. Dr. Etzioni cited a recent report by Draisma et al. (JNCI 2009) which showed that overdiagnosis of prostate cancer was between 23% and 42%.

Findings from the Reduction by Dutasteride of Prostate Cancer Events trial in which the dual 5α-reductase inhibitor dutasteride reduced the risk of biopsy-detectable prostate cancer in men (ages 50-75 years, PSA between 2.5 and 10 ng/mL) at increased risk for developing the disease by 23% compared with placebo were presented. Unlike finasteride, there was not an increase in the prevalence of high-grade disease with dutasteride. Dr. Gerald Andrieu noted that dutasteride enhanced the utility of PSA to detect clinically significant prostate cancer, was well tolerated by the men who took the drug, reduced the risk of precursor lesions, and had beneficial effects on outcome of benign prostatic hyperplasia.
Dr. Eric Klein opened his presentation with a review of the factors that influence risk for prostate cancer. Lifestyle plays an important role and research has shown that high intake of fat, red meats, and dairy and smoking may increase risk, whereas plant-based foods rich in antioxidants may decrease risk. Dr. Klein reviewed the findings of the SELECT study in which 35,533 men ages 50 years or older with PSA <4 ng/ml and a digital rectal exam not suspicious for cancer were randomized to one of four arms: oral selenium alone, vitamin E alone, both agents together, or placebo. The study was discontinued based on a planned interim analysis at year 7 because no detectable benefit from either agent nor any possibility of benefit was shown. The hypothesis of a 25% reduction in prostate cancer was rejected. The formulations and doses of selenium or vitamin E taken separately or in combination did not prevent prostate cancer in this cohort. Criticisms of the clinical trial focused on the choice of the wrong agent, the dosages used, or an incorrect formulation of the agents. Dr. Scott Lippman clarified details of the trial development and lessons learned. He explained that an expert independent committee was convened to discuss the selenium preparation for the clinical trial and that the rationale for the study was based on data showing a 37% reduction in prostate cancer from the Nutritional Prevention of Cancer trial published in 1996. The selection and dose of the vitamin E formulation were based on previously published data in the New England Journal of Medicine showing a 30% decrease in prostate cancer incidence in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study. He concluded by stating that patients who are physiologically deficient in vitamin E and selenium may be the real target populations for this intervention but also stated that other angiogenic and stromal features of the tissues might help guide further therapy with these agents. Other positive elements from these otherwise negative clinical trials point to the fact that an invaluable biorepository of clinical specimens has been created, which is highly annotated for the future.

Energy Balance: From the Bench to the Bedside and Community

Underlying biological mechanisms derived from the rat model of mammary tumorigenesis could potentially explain the relationship between energy balance and breast carcinogenesis. Emerging preclinical evidence presented by Dr. Henry Thompson suggests that a specific threshold of physical activity is needed for breast cancer prevention. In addition, circulating levels of leptin and insulin growth factor I measured in rat mammary models of physical activity are not predictive of the number of tumors in the physically active versus the sedentary group. Further, metformin, a diabetes drug, seems to activate AMP-activated protein kinase in breast tumors and is associated with weight loss and reduced tumor volume. Recent studies indicate that AMP-activated protein kinase activation enhances insulin sensitivity and reduces hyperglycemia by inhibiting hepatic glucose production and increasing glucose uptake in skeletal muscle.

Dr. Pamela Goodwin discussed the epidemiologic evidence for a relationship between energy balance and breast cancer outcomes. Insulin may be predictive of breast cancer recurrence more than body mass index among women, with the overexpressed form of the insulin receptor-α binding insulin as well as insulin growth factor II. Administration of metformin lowers insulin levels by 22% in women diagnosed with triple-negative (estrogen receptor, progesterone receptor, and HER2neu negative) breast cancer; a randomized clinical trial is currently under way to examine the effects of metformin on disease-free survival. When we re-focus our lens on the community, the ever-widening socioeconomic gap in obesity requires immediate attention at multiple levels including economic and health policy.

Collaborations across institutions, community organizations, and neighborhoods are needed with an emphasis on promoting health to the underserved. Nothing less than a multilevel approach to address health disparities and obesity is acceptable given the dismal consequences of obesity on diabetes, cancer, and cardiovascular disease incidence and mortality according to Dr. Tim Byers.

Optical Imaging

Noninvasive optical diagnostic technologies have undergone significant advances since they were experimentally instituted in the 1990s for lung cancer screening. These modalities expand on the principle of using an endoscopy device (e.g., laryngoscope, colonoscope, or bronchoscope) for mucosal surveillance by coupling it to another technology (e.g., autofluorescence cancer detection) to allow for an aided examination that cannot be obtained by the human eye alone.

Dr. Callum Macauley from the British Columbia Cancer Agency described advances in autofluorescence bronchoscopy and optical coherence tomography that allow excision into the bronchialveolar tree to 4th and 5th level bronchi. In these distal bronchi, near histologic quality imaging of these surfaces can now be obtained. This technology is undergoing further developmental use in humans with principal limitations in diagnosing submucosal disease extension when there are no mucosal abnormalities.

High-resolution endoscopic ultrasound could be an important tool in diagnosing pancreatic lesions with high accuracy. However, Dr. Nuzhat Ahmad from the University of Pennsylvania stressed that lesions harboring both inflammation and invasive cancer provide a significant discriminatory challenge, particularly if they are small. Because of the discriminatory difficulty, some patients may have to undergo major pancreatic resection of suspicious lesions, which ultimately prove to be negative for malignancy, encumbering the morbidity of surgery. Of course, the technology allows identification of some patients with early-stage cancers long before clinical presentation, providing an opportunity for survival, which would otherwise be almost impossible.
Multimodal optical imaging technologies have the capacity to aid oral cavity examination for preneoplastic lesions and dysplasias that may be clinically unapparent. Dr. Rebecca Richards-Kortum and colleagues at Rice University in Houston are researching the adaptation of these devices in conjunction with digital 35-mm cameras, which could substitute for more expensive proprietary optics to keep the cost down to practitioners wanting to use the device in their practices, perhaps in a telemedicine type of application (e.g., community dentists).

Further discussion of autofluorescence for the oral cavity was provided by Dr. Catherine Poh from the British Columbia Cancer Research Centre in Vancouver, British Columbia. Dr. Poh introduced the technology and reviewed previous studies conducted in British Columbia with respect to the utility of identifying preneoplastic oral lesions. Her group has coupled the technology with tunable wavelength fluorescence, which has the potential to improve sensitivity for histologically dysplastic areas that appear normal on autofluorescence.

How Can Genetic Information Be Integrated into Primary Care for Cancer Prevention?

Increased knowledge about the genetic factors involved in cancer has been translated into personalized approaches to promote cancer prevention. In most cases, genetic risk information is conceptualized as a factor that will motivate behavior change. However, the research described by Dr. Colleen McBride challenges how genetic risk information is conceptualized in personalized approaches to cancer prevention. In a series of studies that evaluated interest in and responses to genetic testing for lung cancer susceptibility among relatives of lung cancer patients who smoked, only motivation to quit smoking predicted interest in genetic testing, but motivation to quit smoking and actual use of smoking cessation treatments did not differ after genetic testing for GSTM1. These findings could be due to the high level of motivation to quit smoking that was present among participants in this research. At baseline, for instance, the mean level of motivation to quit smoking was 6.44 (SD, 0.98) and 6.35 (SD, 1.11) for GSTM1-present and GSTM1-missing smokers, respectively, using a 7-point scale. These findings help to explain the modest effects of personalized approaches to cancer prevention. That is, if individuals already have high levels of motivation, then the extent to which genetic risk information will increase their desire to make behavioral changes is questionable. As such, we may need to rethink how genetic risk information is conceptualized in personalized approaches to cancer prevention. This research also highlights the importance of evaluating the intermediate pathways that exist in the sequence from providing genetic risk information and behavior outcomes such as smoking cessation, diet, and physical activity. Future analyses of the effect of genetic risk information on behavior change will need to consider the extent to which individuals process risk information effectively and their motivation and confidence to make behavior changes following exposure to genetic risk information. A more refined analysis of these pathways will facilitate the development of more effective strategies for incorporating genetic risk information into cancer prevention programs.

Health Communications and Decision Making

The session on Health Communications focused on issues of health disparities and cancer in underserved populations. Drs. Vetta Sanders-Thompson, Chanita Hughes-Halbert, and Gary Bennett discussed the importance of communities and culture on cancer risk behaviors and interventions. Dr. Sanders-Thompson provided an overview of the multitude of complex issues affecting the development and delivery of culturally sensitive communications including the selection of theories and cultural constructs appropriate to the population.

Few would argue the critical importance of using community-based participatory research to ensure that our science addresses the needs of communities and populations at risk for poorer outcomes. Dr. Chanita Hughes-Halbert's presentation described an ongoing community-based participatory research partnership between community-based organizations and an academic institution in West Philadelphia to assess the needs of the community and to design programs that can address those needs using strategies that fit into the culture and resources of those communities. She highlighted how such community-based participatory research strategies are essential for ensuring that underserved communities ultimately benefit from scientific advances, which has not always been the case to date.

Dr. Gary Bennett's presentation provided a concise integration of many of the previous talks by describing processes and strategies that can contribute to the sustainability of intervention programs in underserved communities. A particularly important point was that rather than trying to force existing community organizations to alter their structure to accommodate an intervention, programs will have a much higher likelihood of successful implementation and sustained development if the intervention is designed to fit into existing structures. His research put these ideas into practice with respect to addressing obesity.

Socioeconomic Status and Health: Developing Pathways, Methods, and Interventions for Reducing Health Disparities

Former National Cancer Institute Director Dr. Samuel Broder once noted that "poverty is a carcinogen," highlighting the fact that individuals of low socioeconomic status (SES) have much higher rates of cancer incidence, morbidity, and mortality. A series of talks elucidated the variety of pathways through which SES can influence cancer risk, and how that risk might be mitigated through targeted intervention and research methods.
The profound adverse effects of traditional indicators of SES on smoking cessation along with alternative indicators of SES, such as subjective perceptions of one's place in the social hierarchy and financial strain, predict cessation over and above the effects of traditional SES indicators, as presented by Dr. David Wetter. Among several racially/ethnically diverse samples of smokers, the investigators showed that SES affects cessation through mechanisms such as neighborhood disadvantage, social support, and stress/ negative affect, with agency serving as consistent proximal determinant of cessation.

Dr. Chyke Doubeni expounded on the role of SES in health disparities from a more macro-perspective that examined the effect of an empirically derived neighborhood socioeconomic deprivation index on mortality and cancer risk behaviors. Tracking over half a million individuals from six U.S. states, their data showed that individuals living in the most socioeconomically deprived neighborhoods had higher risk for death, lower self-reported health, higher body mass index, and poorer diet.

Finally, Dr. K. Vish Vishwanath presented thought-provoking data indicating that there continues to be a substantial "digital divide" with respect to access to the internet and mobile technologies, but that in addition to mere access issues, he also showed problems with usability that are experienced by lower-SES populations. Dr. Vishwanath concluded by noting that although such communication disparities are widespread, they may also be easier to eliminate than some other types of disparities.

**Nutritional Epidemiology and Prevention Trials**


Recent prostate cancer prevention trials have shown similar null effects from selenium methionate and α-tocopherol supplementation in healthy men at high risk for prostate cancer as discussed by Dr. Scott Lippman. The lesson learned from these chemoprevention trials is the need for small preclinical and early-phase clinical studies before the trial that increase our understanding of the underlying cancer biology and the kinetics of pharmaceutical supplements (and dietary food sources as alternatives to supplementation). In the same year as the Doll and Peto article, Walter Merz reported in *Science* 1981 that to improve our understanding of the dose-response relationship of a particular nutrient to the study end point or to an intermediate biomarker of the end point, we should extend the spectrum of small preliminary studies to population-based subgroups representative of different levels of nutritional status because dose-response relationships are likely to be nonlinear.

In considering the role of folate in cancer, Dr. Cornelia Ulrich recommended that we need to consider not only the dose-response relationship but also the window of time in the life course for optimal effects. Indeed, research presented at the "Epigenetics of Aging" Session by Dr. Dana Dolinoy shed light on phenotypic effects from folate in early life. When choline, vitamin B12, and folate supplementation were administered to dams 2 weeks before mating, the fur color of Agouti offspring varied depending on the dose, and similar epigenetic marks appeared when dams were given bisphosphonate A. Yet interestingly, genistein coupled with bisphosphonate A administered before mating counteracted the effects on coat color. Thus, the dose, the window of vulnerability during the life course, and awareness of nutritional supplementation to counteract adverse effects are appearing in the epigenetic research with implications for nutritional epidemiology and cancer chemoprevention.

Dr. Kathy Helzlsouer reviewed the evidence for the relationship between dietary calcium and vitamin D supplementation and cancer prevention. The strongest evidence was for a protective role of dietary calcium supplementation on recurrent adenomatous polyps as demonstrated in a 2009 Cochrane Collaboration Systematic Review. Results from three double-blind, placebo-controlled randomized trials provided no evidence that vitamin D supplementation in the range of 10 to 21 μg/d (400-840 IU) influences the incidence of colorectal and breast cancers or of all cancers. However, recent data from the Third National Health and Nutrition Examination Survey and the Framingham Heart Study in the United States suggest that mortality and cardiovascular events increase with levels of serum 25-hydroxyvitamin D above 40 ng/mL. In addition, a nested case-control study showed a dose response of an increasing risk of pancreatic cancer with serum levels of 25-hydroxyvitamin D of ≥41 ng/mL compared with <32 ng/mL. Until there is clear evidence of benefit, one should aim to achieve a 30 ng/mL therapeutic level and be cautious about supplementing in the high range in the absence of deficiency.

**Conclusion**

An integrative multidisciplinary approach that allows for the translation of promising chemoprevention agents and molecular markers into clinical and epidemiologic investigations for the development of a personalized approach to cancer risk assessment and prevention is critical for advancing the field of cancer prevention. The AACR Frontiers in Cancer Prevention Research meeting provided new avenues for investigation, cautionary notes about the imminent development of trials before preclinical studies, and results from animal research with implications for humans.

**Disclosure of Potential Conflicts of Interest**

P.J. Limburg served as a consultant for Genomic Health, Inc., from August 12, 2008 to April 19, 2010. The other authors disclosed no potential conflicts of interest.