Accumulating data from clinical trials and animal models clearly show that invasive cancer arising at a variety of target organ sites can be prevented, delayed, and/or detected early, thereby leading to enhanced survival in mouse and man alike (1–4). The scientific foundations for cancer prevention and early detection are based on the rapidly evolving understanding of the molecular basis of carcinogenesis as well as the translation of these concepts into clinical trials and, ultimately, strategies that are applicable to the appropriate high-risk populations. Progress in reducing the burden of cancer is predicated on transdisciplinary cooperation among health care providers and researchers from a variety of different fields. One of the main goals of the Sixth Annual AACR International Conference on Frontiers in Cancer Prevention Research was to bring together representatives from these diverse fields and thus promote interdisciplinary interaction and understanding. The conference featured a rich array of sessions, including multiple education sessions, plenary sessions, symposia, poster sessions, organized networking opportunities, and a professional advancement session for young investigators. The Sixth Annual AACR-Prevent Cancer Foundation Award for Excellence in Cancer Prevention Research was presented to Dr. Leslie Bernstein for her pioneering work on the effects of hormones and lifestyle on breast cancer risk. The following summary cannot cover the breadth of the information presented but instead focuses on several of the main themes.

Cancer Risk and Early Detection of Cancer and Premalignant Disease

Predicting cancer risk to identify individuals who could benefit from screening or interventions was a recurrent theme of the conference and the topic of a plenary session. Dr. James Ingle discussed the importance of genetic variation in enzymes involved in the metabolism of drugs used to treat and prevent breast cancer, as well as ongoing work examining whether catechol O-methyltransferase could protect against estrogen genotoxicity through methylation of catecholestrogens. Dr. Stephen Chanock discussed genome-wide association studies that are useful for the discovery of common variants associated with increased cancer risk, including results from the National Cancer Institute Cancer Genetic Markers of Susceptibility studies, which identified prostate cancer susceptibility loci at 8q24. Dr. Miriam Rosin described the Oral Cancer Prevention Program in British Columbia, Canada, that has created an infrastructure combining a province-wide clinician network with a multidisciplinary scientific team to study oral cancer. The Program has developed several approaches to identify early lesions with 20- to 30-fold increased risk of progression to cancer, enabling the early management of such lesions and providing potential markers for measuring efficacy of intervention strategies. Dr. Sharon Manne described an empirically based and theory-driven intervention to increase screening rates among siblings of colorectal cancer patients who have not complied with screening guidelines, showing that personalized behavioral interventions almost double the rate of colonoscopy in this intermediate risk cohort.

Evolution in imaging science, coupled with a greater understanding of molecular targets of carcinogenesis, is providing novel, noninvasive means for cancer detection, management,
and chemopreventive drug development. A plenary session was devoted to imaging premalignant disease and cancer. Dr. Gary J. Kelloff provided an overview of imaging and its promise for detection, diagnosis, and therapeutic monitoring of precancer. Dr. Lawrence J. Marnett discussed targeted imaging of cyclooxygenase-2 using a novel fluorescent imaging agent with preferential accumulation in tumor tissue, allowing direct imaging of cyclooxygenase-2-expressing tumors and intestinal polyps in animals. Dr. Stephen Lam presented a variety of novel optical, endoscopic imaging techniques that may be useful for diagnosis as well as surveillance of premalignant lung lesions, allowing serial monitoring of these lesions without tissue removal. Dr. Mitchell D. Schnall discussed the role of imaging in personalized breast cancer surveillance programs, focusing on technical innovations such as digital mammography, ultrasound, magnetic resonance imaging, positron emission tomography, and 99mTc-sestamibi scintimammography.

Screening for lung cancer, a controversial but important topic, was discussed in a concurrent session. Dr. Jamie Ostroff discussed smoking cessation rates among subjects enrolled in lung cancer screening studies, finding that knowledge of screening results had variable impact on the quit rate, with greater influence among younger smokers. The issue of overdiagnosis by lung cancer spiral computed tomography screening was discussed by Dr. Peter Bach, who cautioned that the current understanding of the natural history of lung cancer may be inaccurate and that longer, randomized screening trials must be completed to determine the true benefit of computed tomography screening. Dr. Christine Berg discussed the National Lung Screening Trial and the potential benefits and harms associated with computed tomography screening. The National Lung Screening Trial has recruited 53,464 current and former smokers to undergo three yearly screenings by spiral computed tomography or chest X-ray. The final analysis for this trial is planned for September 2009. Dr. Amy Berrington de Gonzalez discussed the radiation exposure that results from diagnostic and screening radiographic tests. She estimated that, based on radiation exposure from screening, benefit from screening is not seen until the fifth and sixth decades of life in men and women, respectively, offering no advantage to younger people. Women carry a higher risk of radiation-induced cancer because of routine breast cancer screening.

Targets for Cancer Prevention

Multiple sessions addressed the biology of carcinogenesis and potential targets for cancer prevention. The meeting opened with an introduction by Dr. Andrew Dannenberg, the chairperson of the scientific program committee, who focused on infectious causes of cancer. Dr. Dannenberg discussed successes in reducing hepatocellular cancer rates with hepatitis B vaccination and treatment of hepatitis B infection. He also reviewed the landmark findings leading to decreased cervical cancer incidence, including the development of the Pap smear and the more recent development and approval of the human papillomavirus vaccine. The keynote address was given by Dr. Raymond DuBois, who discussed the importance of inflammation in carcinogenesis, a recurrent theme in this meeting. He focused on the role of cyclooxygenase and prostaglandin (PGE2) pathways in colorectal carcinogenesis, emphasizing that understanding the downstream effector genes and the PGE2 catabolic pathways provides new opportunities to inhibit cancer progression and to design rational combination approaches.

Infectious etiologies of cancer were also discussed in a plenary session. Dr. Silvia Franceschi reported that 18% of cancer worldwide is estimated to be attributable to infectious agents, particularly human papillomavirus, hepatitis B and C viruses, and Helicobacter pylori. She contrasted the relative contributions of viral subtypes in developed and developing countries, discussing the implications for prophylactic programs. Dr. Ming-Wei Yu focused on risk factors for progression to hepatocellular carcinoma in hepatitis B and hepatitis C virus carriers, identifying family history, dual hepatitis B/hepatitis C virus infection, viral load, genotype, and intragenotypic variants as potentially important. Dr. Martin Blaser discussed the role of H. pylori infection in gastric cancer, including the signaling pathways through which the H. pylori cagA protein induces gastric cell proliferation. Provocatively, he suggested that decreased rates of H. pylori infection could account for the increasing incidence of esophageal adenocarcinoma, childhood obesity, and childhood asthma. Dr. Philip Castle discussed the need for improved strategies for cervical cancer prevention and screening, such as carcinogenic human papillomavirus testing. Cost remains a barrier to implementation for those populations at most risk, including women of low socioeconomic status and in developing countries.

A related plenary session focused on the immune system as a target for cancer prevention. Dr. Janice Kiecolt-Glaser examined the link between stress and inflammation, noting that chronic stress can result in chronic inflammation, poor wound healing, and prolonged infectious episodes. High systemic levels of proinflammatory cytokines (e.g., interleukin-6) induced by stress provide a potential mechanistic basis for these observed relationships. Dr. William Nelson discussed inflammation as an etiologic agent for prostate cancer. He reported that nitrosylation of DNA methyltransferase 1 leads to altered CpG island methylation and consequent gene silencing in early prostatic neoplasia, as evidenced by silencing of GSTP1 across the spectrum of early to late prostatic carcinoma. Dr. Lisa Coussens used the K14-HPV16 animal model to dissect the contribution of inflammatory cells to neoplasia. Genetic ablation of mast cells attenuated keratinocyte proliferation and angiogenic vascularization, whereas analysis of B cell–deficient mice revealed a contribution of immunoglobulins. The interaction between B lymphocyte–derived immunoglobulins and Fc receptors on intratumoral mast cells may offer a novel target for therapeutic intervention. Dr. Eric Jacobs reviewed data showing in aggregate that whereas aspirin use is fairly consistently associated with reduced risk of colorectal cancer, results for other common human cancers are weaker. He reported that in the Cancer Prevention Study II Nutrition Cohort, daily aspirin use is associated with an ~15% reduction in cancer risk, mainly due to effects on colorectal, prostate, and, possibly, breast cancer.

The tumor microenvironment, inflammation, and stem cells as targets for prevention were the focus of multiple presentations. Dr. Adriana Albini proposed antiangiogenic therapy as a chemopreventive strategy, focusing on natural compounds that share several common activities—decreasing
inflammation, reactive oxygen species generation, and nuclear factor-κB signaling. Dr. Michael Sporn discussed the use of rexinoids and triterpenoids and their importance in targeting the tumor microenvironment, demonstrating that the effects of these compounds are mediated via multiple pathways and are synergistic. Dr. Jonathan Kurie discussed the use of mouse models to dissect the role of inflammatory cells in lung tumor progression, reporting that the chemokine receptor CXCR2 and its ligands are important for progression of early hyperplastic lesions. Dr. Louise R. Howe discussed the evaluation of a novel combination approach to breast cancer prevention, demonstrating enhanced efficacy with combination of the cyclooxygenase-2 inhibitor celecoxib and the retinoid X receptor-selective retinoid LGD1069. Dr. Timothy C. Wang discussed the importance of inflammation in causing cancer, with changes to the microenvironment and mobilization of circulating progenitors. He showed the requirement for an intact immune system for H. pylori to cause gastric cancer and also showed that chronic inflammation of H. pylori causes repopulation of the stomach with bone marrow–derived stem cells, which then progress to become cancer stem cells and ultimately carcinomas. Dr. Robert Cho discussed breast cancer stem cells, identified as CD44+/CD24−, and the potential clinical utility and ramifications of stem cell theory.

Chemoprevention Clinical Trials
A session on clinical trials presented the results of several recently completed studies. Dr. John Pierce discussed the Women’s Healthy Eating and Living Study, which found that adoption of a diet that was very high in vegetables, fruit, and fiber and low in fat by women with a previous breast cancer did not reduce additional breast cancer events or mortality during a 7.3-year follow-up period. Dr. Frank L. Meyskens presented the results of a phase III trial of the combination of difluoromethylornithine (an ornithine decarboxylase inhibitor) and sulindac in patients with prior colorectal adenomas. The combination significantly decreased the recurrence of colonic polyps with minimal treatment-related toxicity. Dr. Howard Bailey reported the results of a phase III nonmelanoma skin cancer prevention trial with difluoromethylornithine. Although difluoromethylornithine treatment did not significantly reduce the number of new skin cancers in study subjects as a whole, subgroup analysis indicated that the number of new basal cell carcinomas was significantly decreased. Dr. Frank G. Ondrey reported on a phase Ila trial of pioglitazone, a peroxisome proliferator-activated receptor γ (PPARγ) ligand, in oral leukoplakia, which showed a significant clinical response in the majority of participants. Dr. Eva Szabo concluded the session with a presentation on innovative cancer prevention trial design, highlighting the challenges to the field and the importance of conservation of resources and multidisciplinary partnerships.

Obesity and Metabolism
The importance of obesity and metabolism in carcinogenesis is a major research focus and is now beginning to be better understood. In a keynote address, Dr. Ronald Evans discussed the importance of nuclear receptors in regulating systemic physiology, focusing on PPARγ and PPARδ, which have important roles in metabolism and cancer. Endothelial-specific PPARγ ablation resulted in profound alopecia in nursing pups due to secretion of inflammatory mediators into the mothers’ milk, highlighting the anti-inflammatory effects of PPARγ. Dr. Evans then discussed the role of PPARδ in muscle biology, showing that in adult mice, body-wide activation of PPARδ by a pharmacologic ligand increases exercise tolerance only in the context of exercise, not in sedentary animals. These data highlight the complex interactions between tissue-specific effects and the systemic context in regulating specific biological responses.

Speaking at a plenary session devoted to the link between obesity, metabolism, and cancer, Dr. Craig Thompson discussed the connection between cell growth and nutrient signaling, describing how some of the genes most commonly altered during carcinogenesis, such as PI3K and p53, play major roles in nutrient signaling. He presented recent data showing that activation of the cellular energy sensor AMPK inhibits cell growth in the absence but not in the presence of p53. Dr. Stephen Hursting focused on signaling associated with food intake, using a variety of transgenic mice to study the connection between obesity, insulin-like growth factor-I, inflammation, adipokines, and the AKT/mTOR pathway. Dr. Geoffrey Girnun focused on the transcription factor PPARγ, a master regulator of adipocytic differentiation. He discussed the role of PPARγ ligands in cancer prevention and therapy, including in combination with platinum drugs for the treatment of advanced disease. Dr. Tak Mak discussed the role of noncarbohydrate substrates in cancer metabolism, describing how p53 can protect cells from death by inducing CPTIC (a member of the carnitine palmitoyltransferase family), which enables cells to generate energy via β-oxidation of fatty acids.

Tobacco Policy
Tobacco use is one of the lifestyle choices with the greatest impact on cancer. A concurrent session focused on the science of policy-related interventions in tobacco control. Dr. Geoffrey Fong presented the stages of the smoking epidemic in various parts of the world, noting that even in western countries where smoking prevalence has decreased, it will take 15 to 30 years for cancer rates to reflect these decreases. Dr. David Hammond discussed the effect of tobacco product labeling on smoking, commenting that U.S. standards have not been updated since 1984. Tobacco taxes and prices were discussed by Dr. Frank Chaloupka. With any 10% increase in taxes, there is an estimated 4% decrease in smoking across all levels of taxation and incomes, although underage smokers are disproportionately affected. Dr. Chaloupka suggested that tobacco policies could regulate minimum pricing, control internet and duty-free sales, and promote more smoking bans to decrease cigarette use. Dr. Michael Cummings discussed “smoke-free policies,” with increasing numbers of countries and states having implemented smoking bans. Questions remain about the application of bans in lower-income countries and the most effective ways to counter industry efforts to circumvent product regulations. Finally, Dr. Robert Croyle discussed the effect of smoking policy as “cancer related” and suggested that tobacco policies must be flexible to keep up with industry changes and must target all segments of the population, including youth and lower income groups.
Conclusions

The 6th Annual AACR International Conference on Frontiers in Cancer Prevention Research provided an opportunity for researchers from a range of fields to present their data and to establish transdisciplinary collaborations. As the only meeting of its kind to include basic scientists, epidemiologists, clinicians, and behavioral and policy researchers, this conference serves an important role in integrating the diverse fields that are included under cancer prevention. Areas of progress and new questions for investigation were identified. Future developments will build on the foundations established at this meeting.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

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