Meeting Report: Fifth Annual AACR Frontiers in Cancer Prevention Research

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Abstract

Addressing genetics, risk modeling, molecular targets for chemoprevention, clinical prevention trials, behavioral prevention research, public policy, and more, the Fifth Annual International Conference on Frontiers in Cancer Prevention Research, held in Boston, Massachusetts, in November 2006, added an outstanding new chapter to the landmark AACR Frontiers program for advancing the science and practice of cancer prevention throughout the world. [Cancer Res 2007;67(19):8989–93]

Launched in 2002, the annual American Association of Cancer Research (AACR) International Conference on Frontiers in Cancer Prevention Research has become the preeminent cancer prevention research meeting in the world, where multidisciplinary prevention investigators learn about the latest translational and other discoveries from the leading basic, clinical, epidemiologic, and behavioral scientists in the field. Addressing genetics, risk modeling, molecular targets for chemoprevention, clinical prevention trials, behavioral prevention research, public policy, and more, the Fifth Annual Frontiers conference held in Boston, Massachusetts, in November 2006 added an outstanding new chapter to the landmark AACR Frontiers program for advancing the science and practice of cancer prevention throughout the world.

The 2006 program not only featured longer presentations that surveyed various research topics but, for the first time, featured shorter high-impact oral presentations of selected abstracts on primary research that were integrated within thematic sessions. Highlighting a program of extraordinary presentations, Judah Folkman of Harvard University (Boston, MA) gave the Distinguished Lecture on targeting the angiogenic switch in prevention, and Sir Richard Peto of Oxford University (Oxford, England) gave the Keynote Address on the worldwide hazards of smoking. These advances are but the tip of an iceberg of prevention progress portrayed in session formats ranging from educational to career development to topical sessions focused on numerous areas of prime interest, such as those mentioned in the previous paragraph. Because the sessions and oral presentations of this four-day meeting were so extensive, in this report we will highlight only selected major conference topics (tobacco use; diet and diet-related factors; global cervical cancer control in the era of HPV vaccines; angiogenesis; prostate and breast cancer prevention; and challenges of preventive agent development) that reflect themes introduced by the three lectures of the meeting’s Opening Keynote Session (targeting angiogenesis for cancer prevention, worldwide tobacco use and control, and global cancer control strategies).

Tobacco and Cancer

Smoking has been the dominant worldwide cause of cancer for more than a century. This public health problem is defined by (a) an estimated 50% of deaths among smokers being attributable to tobacco, (b) 25% of deaths among smokers occurring in middle age (35–69 years), and (c) dramatic improvement in health outcomes with smoking cessation, even after years of tobacco use. Approximately 50% of cancer deaths in men and 25% in women occur in middle age, largely due to tobacco. Worldwide smoking rates continue to increase, and worldwide tobacco deaths are projected to reach 150 million in 2000 to 2025, 300 million in 2025 to 2050, and more than 500 million in 2050 to 2100 (1). In sum, roughly 1 billion estimated tobacco deaths will occur worldwide in the 21st century, compared with 0.1 billion in the 20th century.

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Stopping smoking markedly reduces health risks. A 50-year prospective study of smoking in British doctors showed that male smokers born between 1900 and 1930 lost, on average, about 10 years of life and that stopping at ages 60, 50, 40, or 30 years resulted in a gain of about 3, 6, 9, or the full 10 years, respectively. A multifaceted approach to reduce tobacco use addressing advertising, warning labels, public smoking, taxes, and pharmacologic strategies is clearly needed. Effective tobacco cessation approaches include demand-reducing measures such as higher cigarette taxes, advertising and promotion bans, warning labels, restrictions on public smoking, and increased access to nicotine replacement and other cessation (e.g., pharmacologic) strategies. Specific recommendations along these lines include (a) instituting a total ban on advertising tobacco products; partial bans have been relatively ineffective, and international data from more than 100 countries support more stringent bans; (b) tripling excise taxes, which potentially would raise 50% more tax dollars for antismoking initiatives and would reduce tobacco consumption by 30%; (c) mandating the use of large packet labels with a tax stamp to counter smuggling; (d) completely banning public smoking; (e) focusing not just on preventing children from starting but also on encouraging adults to quit smoking as well; and (f) de-emphasizing ineffective interventions such as efforts to reduce supply—demand will always create a supply. Regarding tripling excise taxes, data show that every 10% tobacco price increase caused a 3% to 10% decrease in consumption, with more developed countries toward the lower and poorer countries toward the upper end of the range. It has been argued that the reduced demand from this measure would cut cigarette tax revenue to the government (which could be used to fund antismoking initiatives and to cover some smoking-related public health costs), but the data do not support this argument.

Hecht and colleagues are working on approaches for translating basic research into smoking cessation interventions. This group has made important basic discoveries in the area of tobacco-specific carcinogens [e.g., 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)] and DNA adducts, the role of metabolites in NNK activation and detoxification, and the repair of mutagenicity of DNA adducts. In later research focused on biomarker assessments of effects of “regular,” “light,” and “ultralight” cigarettes, they found that smokers of light and ultralight cigarettes do not seem to have a decreased risk of lung cancer versus regular cigarettes (2). This translational work provides a conceptual model for understanding lung carcinogenesis from smoking initiation to various effects (of carcinogens, DNA adducts, and mutations in Ras, p53, and other genes) to lung cancer.

Diet, Diet-Related Factors, and Cancer

Four paradigms have driven research based on the hypothesis that diet plays an important role in carcinogenesis: (a) diet causes cancer through specific genotoxic carcinogens in foods; (b) fat is the most important dietary carcinogen; (c) dietary fruits and vegetables protect against cancer; and (d) energy balance and obesity are major avoidable causes of cancer. Only the fourth paradigm, which is the focus of intense current research, is reported here.

Energy balance and obesity have emerged as a close second to smoking as an avoidable cause of cancer. Intriguing data show body mass index (BMI) increases since 1960 that spiked sharply from 1980 to 2000 (from 10% and 15% to 25% and 35% in men and women, respectively). A host of potential environmental factors are responsible for this increase, including sharp increases in sugared soft drinks, increased prices of fruits and vegetables, and decreased prices of high-fat food and sugar—all linking the trend of increasing BMI to “macro” food policies. Over this time period, food expenditure as a proportion of income was down for home meals but up for meals away from home; meals at fast-food establishments increased (with a clear link to BMI among both high and low income women); and portions at fast-food establishments increased. In addition, food advertising expanded enormously, far exceeding nutrition education efforts of the U.S. Department of Agriculture. In 1997, for example, the U.S. Department of Agriculture spent $333M on nutrition education, whereas McDonalds alone spent $572M on advertising. Furthermore, television watching, a likely indicator of decreased physical activity, increased by more than 300% from 1965 to 1999. Although a number of interventions including work site interventions for weight loss (Healthy Worker Project) or interventions to prevent weight gain over time (Pound of Prevention) were, at best, minimally successful, several promising innovative strategies (e.g., weight awareness involving frequent weigh-ins, food pricing strategies, and portion size education) are in development. In sum, obesity is a severe public health problem requiring a multifaceted approach that includes educational, environmental, and policy strategies.

An American Cancer Society analysis of more than 1 million people (3) found that the proportions of cancer mortality attributable to obesity were 15% in men and 20% in women. Increases in cancer mortality were seen in a wide range of cancers including colon, breast, prostate, and endometrial cancers; renal cell, liver, cervical, and gall bladder cancers; and lymphoma, myeloma and leukemia. There also was a highly statistically significant 8% increase in overall cancer mortality among overweight, but not obese, individuals. Recent data from the National Health service suggest that women with ≥10-kg weight loss have as much as a 60% reduction in postmenopausal breast cancer. There are conflicting data on the influence of obesity on overall prostate cancer risk, but the data on associations of obesity with risks of high-grade prostate cancer and prostate cancer mortality are consistent. Recent studies within the Prostate Cancer Prevention Trial (PCPT; further discussed below) indicated that obese men (BMI ≥30) had an 18% decreased risk of low-grade (Gleason score <7) prostate cancer and a 29% increased risk of high-grade (Gleason ≥7) prostate cancer (versus in men with a BMI <25; ref. 4). In addition, in the large, prospective cohort study called Cancer Prevention Study II, overweight and obesity were associated with an ~20% increase in high-grade prostate cancer, and loss of >11 pounds was associated with a 42% decreased risk of high-grade disease (5).

Global Cervical Cancer Control in the Era of HPV Vaccines

Several prophylactic HPV vaccines composed of HPV type-specific L1 proteins or recombinant HPV virus-like particles (VLP) have been tested in clinical trials (6). Both vaccine types are administered at 0, 1, or 2 and 6 months in a series of three i.m. injections. The target population of either bivalent HPV-16/HPV-18 L1 VLP vaccine (Cervarix, GlaxoSmithKline Biologicals) or quadrivalent HPV-6/HPV-11/HPV-16/HPV-18 L1 VLP vaccine (Gardasil, Merck and Co., Inc.) was healthy young women with no evidence of infection by the HPV targets of the vaccine. Trial
results were based on an intention-to-treat analysis (the bivalent vaccine trial) or on a modified-intention-to-treat analysis (the quadrivalent vaccine trial). The primary end point for both trials was detection of HPV-6, HPV-11, HPV-16, or HPV-18 infections, against which both trials showed efficacy. The bivalent vaccine was 94% [95% confidence interval (95% CI), 61–100] effective in preventing incident cervical HPV-16 or HPV-18 infection; the quadrivalent vaccine was 90% (95% CI, 71–97) effective in preventing persistent HPV-6, HPV-11, HPV-16, or HPV-18 infection. Both vaccines seem to be safe and are well tolerated. The Advisory Committee on Immunization Practices recommended that the HPV vaccines should be given routinely to girls 11 and 12 years old, can be given to girls as young as 9 years old, and are recommended for girls and young women 13 to 26 years old. A major challenge for the broad public health implementation of HPV vaccine is the high cost (more than $300) for the three-dose series. Other challenges include public ignorance about HPV, denial of adolescent sexual activity, and limited availability and cost-effective distribution of the vaccines.

Although HPV vaccines potentially will reduce cervical cancer incidence, some experts still recommend screening for precancerous lesions because current vaccines will not protect against all HPV types, including some associated with cervical cancer risk. These vaccines could lead to a screening deficit, which could be addressed by an algorithm based on screening for HPV and cytologic triage. There is great interest in the use of HPV tests for early detection in population screening and triage. Substantial evidence supports HPV testing. Usually, HPV testing has 20% to 40% greater sensitivity but 5% to 10% lower specificity than does pap cytology for detecting cervical high-grade lesions or cancer (7). HPV testing is a well-validated assay and is less prone to subjectivity in interpretation compared with pap cytology. The rational use of HPV testing in conjunction with cytology is becoming an increasingly sensible approach for creating a surveillance system to monitor the epidemiology of HPV infection in the era of HPV vaccination. HPV testing and vaccines also may have applications for preventing oropharyngeal and other cancers (8).

Angiogenesis

A number of thematic sessions focused on different biological processes critical to carcinogenesis and cancer prevention. These processes included tissue injury/repair, inflammation, the epithelial-mesenchymal transition, genetic instability, and many more. In this review, we highlight angiogenesis, which was reviewed by Dr. Folkman in the Keynote Address and by others in smaller sessions during the meeting. Folkman and colleagues observed more than three decades ago that tumor growth was severely restricted in the absence of angiogenesis. This and other results led to the proposal that solid tumor growth depends on new capillary sprouts, or angiogenesis, without which solid tumors can become completely dormant. Therefore, angiogenesis became a therapeutic target and, more recently, a potential target for chemoprevention as well.

Preclinical and clinical studies have validated angiogenesis as a therapeutic target for advanced cancers in recent years. The vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) axis seems to play a central role in tumor angiogenesis, and VEGF and VEGFR are the best-studied angiogenic factors to date (9). Preclinical mouse studies showed that some premalignant lesions experience an “angiogenic switch” early in carcinogenesis, reflecting a change in the net balance between angiogenic stimulators and inhibitors. VEGF and matrix metalloproteinase-9 were shown to play important roles in the angiogenic switch in these models. Data also suggest that different populations of circulating cells (including endothelial progenitors, hemangiocyte and pericyte progenitors, and a variety of inflammatory cells) may contribute to the angiogenic switch and thus themselves may be targets for chemoprevention (10). Antiangiogenic agents delayed the formation of pancreatic islet carcinoma in a murine model (11). Mammary cancer cells implanted in a rat induced angiogenesis long before the tumor population reached the limiting size (0.2–2 mm) of a nonneovascularized tumor. Concomitant implantation of these mammary cancer cells with a truncated soluble VEGFR led to tumor cell apoptosis, tumor regression, and suppression of tumor growth before the appearance of neovascular sprouts. In vitro, however, this receptor had no effect on tumor cells, although it had a potent antiproliferative effect on endothelial cells. These and other preclinical studies suggest that angiogenesis is an early and critical step in tumorigenesis, and that antiangiogenic agents may inhibit tumor progression and growth.

Data from human clinical specimens further suggest that angiogenesis begins during preinvasive carcinogenesis. For example, an initial mild increase in vessel density can occur in early dysplastic cervical intraepithelial neoplasia (CIN) I. The dense opposition of new vessels along basement membrane underlying dysplastic epithelium denotes an obvious angiogenic switch in CIN II and CIN III. Pneoplastic lung lesions ranging from hyperplasia and metaplasia to carcinoma in situ are associated with increased microvessel density in the surrounding mucosa. Bronchial pneoplastic lesions express elevated levels of VEGF, epidermal growth factor receptor (EGFR), and cyclooxygenase-2, but no specific angiogenic stimulator has been established.

The overall preclinical and clinical data support chemopreventive targeting of angiogenesis through the VEGF/VEGFR axis. Pharmacologic approaches to inhibit the VEGF/VEGFR axis include monoclonal antibodies (directed either against the ligand or the receptor), soluble binders of VEGF, antisense oligonucleotides to VEGF, VEGF tyrrosine kinase inhibitors, and ribozymes against VEGFR mRNA (9). Only the anti-VEGF monoclonal antibody bevacizumab and the VEGF tyrrosine kinase inhibitors sorafenib and sunitinib are currently approved for the treatment of advanced cancers (including colorectal, renal cell, and non–small cell lung cancers). Although generally well tolerated, these drugs can cause rare serious adverse events (grade 3 or 4 bleeding, thromboembolic, and cardiovascular events) that are potential obstacles to their use in chemoprevention. ZD6474 is another promising VEGFR-targeted drug for cancer treatment and perhaps prevention. This agent blocks both EGFR and VEGFR tyrrosine kinase inhibitors sorafenib and sunitinib and is currently being tested in patients with advanced non–small cell lung cancer, medullary thyroid cancer, and adult gliomas.

Cancer Chemoprevention

The conference presented several sessions on chemoprevention research in various organ sites including the colon-rectum, pancreas, head and neck, skin (melanoma), gynecologic sites, breast, and prostate. This report will focus on research in the breast and prostate because the major advances of clinical cancer prevention have occurred in these two sites.
The Prostate Cancer Prevention Trial (PCPT) tested the 5α-reductase inhibitor finasteride (versus placebo) in 18,882 randomized men ≥55 years old and with a baseline normal digital rectal examination and prostate-specific antigen level of ≤3.0 ng/mL. Finasteride produced a 24.8% relative risk reduction in the 7-year period prevalence of prostate cancer (versus placebo; 24.4% versus 18.4% prevalence, \( P < 0.001 \)). However, an increased risk of high-grade prostate cancer also occurred in the finasteride versus placebo arm (6.4% versus 5.1%, \( P < 0.005 \); ref. 12). Subsequent analyses have revealed that finasteride significantly increases the sensitivity of prostate-specific antigen for detecting overall and high-grade prostate cancer and of digital rectal examination for detecting overall prostate cancer. In addition, PCPT data on radical prostatectomy, which is the gold standard for prostate cancer grading because it is not subject to biopsy sampling error, indicated that high-grade disease was not significantly increased in the finasteride arm (versus placebo; ref. 13). Although a true increase in high-grade disease in some patients cannot be ruled out, it does seem that the initial report underestimated the potential for finasteride to decrease the prevalence of prostate cancer and overestimated the risk of high-grade disease.

The main reason that the PCPT was so large and took so long to complete is that it did not have the ability to identify and select truly high-risk participants. One of the most important aspects of the PCPT was the creation of a biorepository, which includes sera from all of the participants and lymphocytes and prostate tissues from many. This specimen resource, which is linked to a large clinical database, has provided a unique opportunity to explore the biology of prostate cancer and to identify genetic, metabolic, and environmental factors associated with a high (or low) risk of prostate cancer, especially high-grade prostate cancer, and with the efficacy of finasteride (14).

The selective estrogen receptor modulators tamoxifen in the Breast Cancer Prevention Trial (15) and raloxifene in the STAR (16) greatly reduced estrogen receptor (ER)–positive breast cancer development, for which they are FDA approved, but these agents have no effect in preventing ER-negative breast cancer. Therefore, a major focus of breast cancer prevention research is novel strategies for preventing ER-negative breast cancer, which accounts for up to 30% of all breast cancers.

It is clear that not all endocrinologic risk factors for breast cancer (such as parity, age, hormone use, and estrogen blood levels) apply equally to ER-negative and ER-positive breast cancers. Advanced age is more highly associated with ER-positive breast cancer, as is a history of using postmenopausal hormones. Low folate intake, particularly in women with a high alcohol intake, is associated with an increased risk of ER-negative breast cancer. These collective findings suggest that the risk factors for ER-positive and ER-negative breast cancers are distinct from one another.

Overexpression of EGFR, activated erbB2, RAF, or mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase kinase (MEK), causes ER-positive MCF7 breast cancer cells to convert to ER-negative cells. Conversely, ER-negative cells with activation of these pathways can be converted to ER-positive cells by inhibiting these signal transduction pathways (by inhibiting MAPK or inhibiting EGFR activity). The same effects can occur in human primary tumor explants. A subset of ER-negative tumors can be converted to ER-positive tumors by blocking EGFR or MEK. Previously ER-negative primary breast tumors that reexpress ER become sensitive to the growth inhibitory effects of tamoxifen. These studies suggest that it may be possible to treat or prevent ER-negative breast cancers by reactivating the expression of ER in premalignant lesions or subclinical cancers (by the use of signal transduction inhibitors) and then treating with antiestrogens to prevent the emergence of clinical breast cancer. Promising new agents for the prevention of ER-negative breast cancer include retinoid X receptor–selective retinoids (rexinoids), triterpenoids, and EGFR inhibitors, which have shown preclinical activity as single agents and in various combinations and continue to be in preclinical and clinical drug development.

There are exciting new data showing that breast cancers arising in BRCA1-mutant mice (which are typically ER-negative) are sensitive to antiprogestrone treatment. In a novel mouse model of BRCA1 tumors, wherein both the p53 and BRCA1 tumor suppressor genes are inactivated in mammary tissue, the mammary glands overexpress the progesterone receptor and treatment with a progesterone antagonist prevented mammary tumorigenesis (17). These findings suggest that it may also be possible to prevent breast cancer in women carrying BRCA1 mutants using antiprogestrone drugs.

### Challenges of Preventive Agent Development

Chemopreventive drug development is highly complex and difficult to achieve. Challenges to testing promising agents in early clinical trials include the need for validated biomarkers of efficacy and high risk (14, 18). Other significant challenges to preventive agent development include regulatory challenges such as the lengthy regulatory approval for investigational new drug applications and new drug applications, the issues of labeling indications for cancer risk reduction as opposed to cancer prevention, and the need for post-marketing surveillance for potential rare toxicities of chemopreventive agents. Changes in the regulatory environment, including defining acceptable chemopreventive toxicity, changing patent law (to extend the length of patents for drugs developed for prevention uses), and refining laws regulating liability for rare chemopreventive side effects, will be necessary before the pharmaceutical industry puts a major effort into developing cancer-preventive agents (19, 20). The enormous costs of definitive phase III prevention trials, which can cost up to more than $100 million, cloud the future of these important trials.

### Conclusions

The Fifth Annual AACR Frontiers in Cancer Prevention Research conference succeeded in advancing the science and practice of cancer prevention on many fronts besides the few selected for attention in this meeting report. Investigators from every corner of the world and every prevention discipline came together to report on and learn about the latest developments in the full spectrum of research areas noted at the beginning of this report. Judah Folkman and Sir Richard Peto led an extraordinary group of established and younger presenters in a rich variety of session formats including keynote, plenary, educational, organ site, and poster sessions. This Frontiers Conference fostered collaborations between all the disciplines of prevention research; promoted public, academic, government, and industry awareness of the importance of cancer prevention science; and catalyzed coordinated, focused, transdisciplinary research efforts that promise to accelerate the contributions of cancer prevention to science and the public health.

It is virtually impossible to adequately convey in a meeting report format the extraordinary breadth and depth of all the work.
that was reported in the 44 richly varied sessions and nearly 180 slide and 400 poster presentations of the 2006 conference. Nevertheless, we earnestly hope that the “sampler” provided here succeeds in conveying the excitement and richness of not only the Fifth Annual AACR Frontiers in Cancer Prevention Research conference but also of the earlier four and, we are confident, of those yet to come.

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