[CANCER RESEARCH 63, 5649–5655, September 15, 2003]

Review and Meeting Report

Frontiers in Cancer Prevention Research[1]

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Introduction

In October 2002, the AACR pioneered and hosted the first major annual meeting devoted to cancer prevention. This signal event marked the rapid movement of cancer prevention to the forefront of feasible modalities for reducing the burden of cancer. Within only the past five years, the Food and Drug Administration issued its first two expressly chemoprevention-related approvals, one of tamoxifen for reducing breast cancer risk (1), the other of celecoxib (2) in the setting of FAP.[3] Abundant other signs also reflect a sea change in cancer prevention. Recently reported studies demonstrated the ability of finasteride to reduce prostate cancer development and of NSAIDs to reduce the burden of sporadic adenomas (3–5). Molecular cancer risk assessment and cancer-risk-reduction surgery have become standard approaches (6, 7). Traditionally treatment-oriented institutions (cancer centers and National Cooperative Oncology Groups) are leading seminal cancer prevention trials (1–3, 5). There has been a paradigm shift in oncology from cancer treatment toward cancer prevention, mirroring a similar decades-old shift in cardiology. To reduce the risk of myocardial infarctions, it was necessary initially to identify the prominent risk factors and test preventive interventions. This process led to a better understanding of, educating the public and health-care practitioners about, and developing interventions that effectively modulate many cardiovascular risk factors (*e.g.,* hypertension, hyperlipidemia), which have come to be considered bona fide diseases. This transition from "risk factor" to "disease" reveals a subtle evolution in our definitions of health and disease. Whereas traditional disease concepts focused narrowly on obvious symptomatology, newer concepts recognize that most illnesses, including cancer, have long, clinically silent ramping-up phases of evolving molecular and cellular aberrations. Therefore, the science and medicine of cancer prevention challenge our traditional definition of disease, demanding a subtler view composed of formerly defined risk factors that can be treated preventively over sustained periods.

The AACR prevention meeting brought together academic, government, industry and advocacy-group leaders to focus on a comprehensive agenda of prevention disciplines, such as chemoprevention, risk-reduction surgery, behavioral science and health services research, diet and nutrition, molecular genetics, epidemiology, and imaging. Extraordinary advances in the molecular biology of cancer susceptibility and carcinogenesis have raised important opportunities (even the responsibility) to apply this biology to the multidisciplinary development of novel clinical cancer prevention approaches. A wave of new technology (*e.g.,* high-resolution endoscopy, laser-capture microdissection, multiplex gene/expression/protein arrays and small interfering RNA) is rapidly increasing our understanding of neoplastic evolution. We now understand that this process involves mutations in key tumor suppressor genes and/or oncogenes, epigenetic changes via aberrations of histone acetylation or DNA methylation, genetic instability, and defects in signal transduction (7–9), with clonal expansion (10) and, remarkably, intraepithelial spread/metastasis of premalignant cells (11). Through cross-sectional and prospective validation, these molecular alterations can be used as (*a*) markers of cancer risk and susceptibility to carcinogenesis, (*b*) targets for developing novel preventive interventions, and (*c*) intermediate measures of response that can help in identifying and developing new cancer chemopreventive agents (12). This article reviews important areas and future directions of the new science emerging in the field of cancer prevention and presented during the first AACR Cancer Prevention conference.

Genetics and Molecular Epidemiology

Studies of genetics and molecular epidemiology are increasing our understanding of inherited susceptibility to carcinogenic exposures and interindividual variability in this susceptibility. The study of gene-gene and gene-environment (diet, diet-related factors, growth factors, hormones) interactions is a major component of this work. Genetic variants regulating steroid hormone metabolism (*e.g., SRD5A2*, *CYP17*) may partly explain ethnic differences and interindividual variability in hormone-related cancer risk (13, 14). The development of tobacco-related cancer only in subsets of smokers now can be explained, in part, by genetically mediated differences in tobacco carcinogen activation (15). Genetic polymorphisms that interact with dietary exposures to increase cancer susceptibility have been identified (16). This new knowledge will facilitate the design of novel prevention approaches for targeting tailored interventions on specific genotypes.

Preventive pharmacogenomics is a new field that increases our understanding of interindividual variability in agent response attributable to inherited variations in drug metabolism and molecular drug targets (17–20). The preventive activity of isotretinoin in head and neck carcinogenesis may depend on *cyclin D1* genotype (18), aspirin activity in colorectal neoplasia may depend on specific polymorphisms of *CYP 2C9* (19), finasteride activity in prostate cancer may depend on polymorphisms of *SRD5A2* (3, 13) and tamoxifen may

Received 7/23/03; accepted 8/11/03.

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[1] This work was supported in part by Cancer Center Support Grant CA16672 from the National Cancer Institute, NIH. This article reports on the AACR conference "Frontiers in Cancer Prevention Research: Genetics, Risk Modeling, Molecular Targets for Chemoprevention, Behavioral Prevention Research, Clinical Prevention Trials, Science and Public Policy," held in Boston, MA, October 2002, chaired by Waun Ki Hong, M.D., and co-chaired by Raymond N. DuBois, Ph.D., M.D., Brian E. Henderson, M.D., Caryn E. Lerman, Ph.D., and Scott M. Lippman, M.D.

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[3] The abbreviations used are: FAP, familial adenomatous polyposis; COX-2, cyclooxygenase-2; EGFR, epidermal growth factor receptor; LOX, lipoxygenase; PPAR, peroxisome proliferator-activated receptor; NSAID, nonsteroidal anti-inflammatory drug; IEN, intraepithelial neoplasia; SERM, selective estrogen receptor modulator; IGF-1, insulin-like growth factor; SELECT, Selenium and Vitamin E Cancer Prevention Trial; HPV, human papillomavirus; NCI, National Cancer Institute; PCPT, Prostate Cancer Prevention Trial; ER, estrogen receptor.

reduce breast cancer risk in *BRCA-2* but not *BRCA-1* mutation carriers (20). Tamoxifen is metabolized by SULT1A1, CYP2D6, or CYP3A4, which may affect its bioavailability or the generation of metabolites associated with adverse events. Chemopreventive studies may not detect positive effects of preventive agents that work only in a study-population subset characterized by a specific genotype. Another example of a pharmacogenomic approach to cancer prevention is the potential tailoring of smoking-cessation pharmacotherapies based on smokers' genotypes (21).

Research in genetics and molecular epidemiology also is linked tightly with surgical risk reduction approaches. Prophylactic resection of high-risk tissue in certain germ-line mutation carriers, including prophylactic thyroidectomy in patients with MEN2a, MEN2b, familial medullary thyroid carcinoma, or Ret mutations, bilateral mastectomy and oophorectomy to reduce breast cancer risk, and ovarian cancer risk in carriers of *BRCA1* and *BRCA2* mutations, and colectomy in patients with FAP and hereditary nonpolyposis colorectal cancer (HNPCC; Refs. 22–24), have become a standard albeit radical form of prevention or risk reduction. Novel statistical approaches are being developed for modeling cancer risk and the potential efficacy of surgical risk reduction (25). As is discussed in more detail in the Behavioral Science Research Section, behavioral-science and health-services studies complement genetic and molecular epidemiology in developing clinical approaches for reducing cancer risk in susceptible populations. Assessing surrogate/target-tissue biomarker correlations in carcinogenesis are important new areas of molecular epidemiology (18, 26).

Biomarkers/Early Detection

A primary area of biomarker research is the prevention of tobacco-related cancers (27). Metabolically activated forms of these carcinogens form DNA adducts that can cause permanent critical gene mutations leading to the loss of normal growth control mechanisms. Chronic exposure to tobacco results in a constant barrage by over 60 carcinogens on DNA, promoting multiple genetic changes leading to cancer. Specific biomarkers and methods are now available for quantitating the cellular uptake of a variety of tobacco carcinogens and the associated formation of DNA-binding fragments and adducts (28).

The early detection of cancer and identification of high-risk IEN are major priorities for cancer research. This work includes the identification of molecular aberrancies in exfoliated cells and the use of novel imaging technologies (29). A variety of assays might facilitate the identification of genetic and epigenetic alterations. These approaches could include the use of microsatellite, mitochondrial DNA, and promoter-methylation analyses of easily collected specimens (*e.g.,* in saliva and urine; Ref. 30). Proteomic analyses may play an important role in early cancer detection and chemoprevention in high-risk groups (31). Lessons learned from recent studies of prostate-specific antigen (PSA) for early detection of prostate cancer underscore the importance of carefully planned biomarker discovery, development, and validation studies such as those in the NCI Early Detection Research Network (12). The AACR formed the Task Force on the Treatment and Prevention of IEN to address the crucial issue of IEN end points for chemoprevention trials (32). A new prevention task force has been formed to build on the IEN Task Force and focus on molecular markers of cancer risk, early detection, and preventive (surrogate-end-point biomarkers) activity (7, 33, 34).

Molecular Targeting in Chemoprevention

In the past, chemotherapy involved mainly toxic i.v. drugs, and chemoprevention mainly vitamins and minerals (35). A revolution in drug development has been sparked by molecular targeting research that has led to the development of many promising new drugs (*e.g.,* oral drugs that are low in toxicity) applicable to prevention and/or therapy. There is intense interest in studying the chemopreventive potential of molecular-targeted drugs such as EGFR inhibitors, SERMs and aromatase inhibitors, which initially were used as cancer therapy (36). Conversely, agents such as COX-2 inhibitors that have been studied in cancer chemoprevention are now under active study for cancer therapy. In many instances, molecular-targeting agents may be developed both for cancer therapy and prevention within the same Phase I/II trials assessing toxicity and optimal biological dose. Identifying multiple molecular targets for effective combinations of preventive agents is a major focus of chemoprevention study (37).

Developing targeted drugs for prevention involves a number of complicated signaling pathways/targets [*e.g.,* LOXs, protein kinase G (PKG), PPARs, activator protein-1 (AP-1), nuclear factor-κB (NF-κB), signal transducer and activator of transcriptions (STATs), p53, MMPs, GSK3β, Akt] and approaches (*e.g.,* receptor tyrosine kinase inhibitors, demethylating agents, histone deacetylase inhibitors, antisense molecules, and gene therapy) and determining the effects of active agent classes, including complicated cross-target effects (*e.g.,* "selective" COX-2-inhibiting NSAIDs) and cross-organ site (*e.g.,* estrogens in prostate carcinogenesis effects; Refs. 36–45). For example, the preventive activity of NSAIDs may be mediated via molecular target mechanisms other than COX-2, such as PKG, 15-LOX, and PPARs (44, 45), which, therefore, serve as new potential targets for drug development. The loss of normal apoptotic mechanisms is a hallmark of cancer development, and, therefore, targeting apoptosis-inducing molecules is a high priority of preventive agent development (46). Gene-based animal model development (*e.g.,* tissue-specific, temporally regulated transgenic, dominant-negative, and knockout models) will be a valuable tool for decoding the complicated tissue-specific mechanisms of action of different preventive agents (47). Preclinical studies of UVB- and UVA-signaling pathways have identified several potential new targets, including AP-1, COX-2, p38 mitogen-activated protein (MAP) kinase, and phosphatidylinositol 3′-kinase (PI3K), for skin cancer prevention (48, 49).

Potential preventive agents such as natural products and their derivatives and synthetic analogues are being identified from terrestrial (*e.g.,* EGFR inhibitors, protease inhibitors, new triterpenoids, dietary polyphenols, green tea, resveratrol, and curcumin) and marine plants, and soil organisms (38, 49–51). A recent study found that the natural plant product deguelin has potent apoptotic effects in premalignant lung cells through the suppression of the phosphatidylinositol 3′-kinase (PI3K)/Akt pathway (52).

The study of retinoids in head and neck carcinogenesis provides a molecular model of the principle that chemoprevention agents can delay the onset of clinically detected cancer. Mechanisms of cancer delay may involve suppression of genetic instability (53) and detouring multistep carcinogenesis down alternate molecular pathways (54). A recent translational study suggests that retinoic acid produces head and neck cancer delay via a molecular detour at 11q13 (*cyclin D1*; Ref. 18).

Clinical Chemoprevention

Findings from clinical cancer chemoprevention trials have contributed to the maturation of cancer prevention in general. Early trials of retinoids in preventing skin and head and neck cancers provided the proof of principle for chemopreventive approaches (35, 36, 55–58). "Standard" regimens in the arsenal of chemoprevention that have been in use for some time include hepatitis B vaccine to prevent liver cancer (59), *Bacillus Calmette-Guérin* (BCG) and valrubicin to treat bladder IEN, topical 5-fluorouracil, diclofenate, masoprocol, and ami-

nolaevulinic acid (with photodynamic therapy) for treating skin IEN (32, 54). These prevention gains were consolidated by more recent results from several prospective chemoprevention studies such as tamoxifen for breast cancer prevention [National Surgical Adjuvant Breast and Bowel Project (NSABP) P1 (Breast Cancer Prevention Trial) and B24 and The International Breast Cancer Intervention Study (IBIS); Refs. 60–62], sulindac or celecoxib for reduction of colonic polyp burden in FAP, aspirin or calcium for reducing sporadic adenoma risk (2, 4, 5, 63–65), and finasteride for reducing prostate cancer risk (3).

As illustrated by hepatitis B vaccine to prevent liver cancer (59), vaccines are an important area of development with high clinical potential for cancer prevention. For example, persistent HPV infection in the cervix is linked to the development of cervical intraepithelial neoplasia and cancer, and virtually all cervical cancers are HPV DNA positive. Therefore, developing vaccines against HPV would represent a unique chemoprevention approach (66) because data suggest that the majority of vaccinated women develop high HPV antibody titers. Defining specific antigens and immunization protocols that could effectively prime the immune system to eliminate cancer before its clinical manifestation is an intriguing approach. A major focus of vaccine development for cancer prevention is targeting antigens differentially expressed by cancer or IEN cells but not by normal cells. For example, the antigens MUC1 (expressed in polyps but not in normal colon cells) and cyclin B1 (aberrantly expressed by tumor cells; Refs. 67 and 68) might be important targets for development of an effective vaccination against colon IEN and cancer.

Although Food and Drug Administration-approved in three breast-cancer prevention settings, tamoxifen illustrates the imposing challenge in disease prevention of balancing complex agent risks and benefits. Tamoxifen risks include endometrial cancer and pulmonary embolism. Strategies for improving the risk-benefit ratio of tamoxifen (*e.g.,* by lowering the dose) are under investigation (69). Models estimating an individual's breast cancer risk and potential benefits and the risks of intervention with tamoxifen are a challenge to incorporate into clinical practice (61). Current evidence suggests that tamoxifen, other SERMs, and other hormone-directed agents do not prevent ER-negative breast cancers. Several agents, *e.g.,* RXR-selective retinoids, COX-2 inhibitors, EGFR inhibitors, can suppress the development of ER-negative breast cancer in animals (61, 70), and a combination of these and ER targeting agents may prove to be the most effective strategy to prevent breast cancer in the widest possible population of women at risk.

In lung cancer chemoprevention, clinical and preclinical mechanistic studies found a harmful interaction of β-carotene with cigarette smoke (36). Recent study has focused on high-risk former smokers (71) and has produced some promising early results (27, 72). Study of the metabolism of tobacco carcinogens has led to chemoprevention trials with carcinogen-DNA adduct end points. Consistent with the prevention-therapy overlap discussed above, recent lung-cancer prevention approaches include the use of farnesyl transferase inhibitors or EGFR tyrosine kinase inhibitors to reverse IEN in patients with a history of smoking-related cancers. New methods of agent delivery, such as aerosolized inhalation, may improve the therapeutic index of preventive agents in accessible organs such as the lung (73).

Prophylactic colectomy is the standard treatment for patients with FAP, chronic ulcerative colitis (CUC), and, to a lesser extent, HNPCC. The timing of surgical resection depends on the presence of high-grade dysplasia in CUC, and the extent of adenoma burden in FAP, but the extent of resection in FAP is controversial. Morbidity of colectomy is high, and focus on alternative preventive interventions has led to randomized controlled trials of the nonspecific COX inhibitor, sulindac, and the COX-2 inhibitor, celecoxib, which were shown to reduce colonic polyp burden in patients with FAP (2, 63). Oxidative metabolism of the omega 6 polyunsaturated fatty acid (PUFA) arachidonic acid by COX-2, and 5- and 12-LOX-mediated pathways has been linked to tumorigenesis in animal models and in humans. PUFA metabolism exists in a dynamic balance that shifts during carcinogenesis to 5- and 12-LOX and COX-2 pathways and away from 15-LOX-1 or -2 pathways, the products of which appear to be anticarcinogenic (45, 74, 75).

Prostate cancer prevention is a major focus of clinical chemoprevention (41, 76, 77). Presented while still ongoing during the AACR Frontiers conference, the landmark Southwest Oncology Group (SWOG)-led NCI Intergroup PCPT was stopped early and reported in July 2003 (3). The PCPT tested the 5-α-reductase-targeting agent finasteride *versus* placebo for 7 years in 18,882 men, ages $\geq$55 years. Finasteride produced a 24.8% reduction ($P < 0.001$) in the period prevalence of prostate cancer. More men developed high-grade tumors (Gleason scores $\geq$7) in the finasteride arm (6.4%) than in the placebo arm (5.1%; $P = 0.005$). Urinary symptoms/events related to benign prostatic hypertrophy were more common in men on placebo, whereas sexual side effects were more common in men on finasteride. Therefore, men considering finasteride for prostate cancer prevention must carefully evaluate the possible benefits of prostate cancer risk reduction and reduced urinary problems against increased sexual side effects and potential risks of high-grade disease. The SELECT is an ongoing trial testing selenium and vitamin E in a 2×2 factorial design based largely on provocative secondary analyses of the two agents in prior NCI Phase III prevention trials (selenium tested in skin cancer prevention; vitamin E in lung cancer prevention) (36). The accrual goal is 32,400 men at risk for developing prostate cancer because of age (African Americans, $\geq$50 years; other men $\geq$55 years). Activated in July 2001, study accrual is 75% complete in only 2 years. Both the SELECT and PCPT have invaluable biorepositories (*e.g.*, serum, WBCs, and malignant and nonmalignant prostate tissue) for translational molecular studies of prostate carcinogenesis, cancer risk, and intervention effects (78).

Nutritional and Energy Balance

Epidemiological studies have identified at-risk populations and potential interventions associated with reduced cancer risk. The results of these studies are important for generating prevention hypotheses (79) but should be confirmed in rigorous randomized controlled trials before public health recommendations are made (80). Epidemiology has linked diet and diet-related factors, *e.g.*, obesity, to cancer risk and prevention. Preclinical studies are shedding new light on the relative contributions of dietary fat, obesity, caloric restriction, and exercise to cancer risk (81, 82). In particular, recent studies have shown that moderate caloric restriction delays mammary tumor development and death in genetically predisposed mice. Data suggest that endocrine mechanisms, such as IGFs/insulin resistance, may mediate these effects. IGF-1 is a key regulator of the endocrine, paracrine, and autocrine-signaling network that controls energy metabolism and has been linked to risk of certain cancers, including advanced/aggressive prostate cancer (83). Further understanding of IGFs as a marker of cancer risk and prevention will be important.

Based on epidemiologic data (84), low-fat, high-fiber and fruit-and-vegetable diets have been tested in recent randomized sporadic adenoma trials (85, 86), which, although negative, underscore the evolution of the epidemiology of diet and nutrition. Basic science assessments of nutrition and energy balance and interactions in cancer development or prevention will be critical to advances in the field.

Behavioral Science Research

Tobacco control remains our greatest challenge (87). In 2002, tobacco was responsible for over 4 million deaths, and it is predicted that in 2030, more than 10 million tobacco-related deaths will occur worldwide, 7 million in developing countries. In the United States alone, tobacco is responsible for more than 100 billion dollars in annual economic costs. The future of cancer prevention also depends heavily on study determinants of health-behavior changes and evaluation of interventions to improve the outcomes of and participation in cancer prevention programs.

Behavioral science and health services investigations are vital to advance the science of cancer prevention and to identify the optimal ways to apply these advances in practice to reduce cancer risk. One important area of behavioral science seeks to elucidate the determinants of cancer risk behaviors, including interacting biological, behavioral, and social factors. Emerging research in this area is identifying genetic polymorphisms that increase the likelihood of smoking initiation and addiction to nicotine (88–90) and that moderate the efficacy of tobacco control interventions (91). The genetic underpinnings of other cancer risk behaviors, such as alcohol use (92) and obesity (93) are also being elucidated. Advances in our understanding of the behavioral, social, and cultural bases of tobacco use, eating behavior, and physical activity will also greatly facilitate the development of improved interventions for behavioral risk factor reduction (94–96).

Behavioral science and health services research complement research in genetic susceptibility to cancer. Our ability to identify individuals who carry cancer susceptibility mutations brings responsibility to obtain adequate informed consent and education (97–102). One important contribution of behavioral science research has been to provide empirical evidence that the majority of participants who receive genetic testing for cancer susceptibility do not suffer significant adverse psychological consequences (100); however, genetic testing may generate specific stresses related to the testing process (101, 102) or may lead to significant distress in subgroups of vulnerable participants (103). Moreover, until cancer-predisposing alterations can be corrected at the molecular level, there is a need to enhance adherence to early cancer detection in persons identified as mutation carriers (104–106). It is possible that communicating genetic risk to individuals will motivate changes in cancer-related behaviors, such as tobacco use; however, much remains to be learned in this area (107, 108). Of course, to realize the full potential of new behavioral prevention and chemoprevention interventions, participation and long-term behavioral compliance are key (102, 109, 110).

The successful translation of cancer prevention research also requires an adequate understanding of several issues addressed by health services research. For example, research is elucidating factors that influence decisions to participate in genetic testing, and decision-making about detection and risk reduction strategies for which a firm base of evidence has not yet accumulated (99, 111). New information is also emerging regarding the economic and quality-of-life outcome of genetic testing and cancer prevention approaches (112, 113). Research has also identified potential barriers to the effective and ethical translation of cancer prevention research, including a lack of provider readiness (114). A proactive approach to addressing these barriers is essential to promote the diffusion of science-based cancer prevention approaches.

Future Challenges and Directions

Cancer prevention must overcome substantial obstacles and challenges unique to this field. Low participation by minority and medically underserved populations (115) remains a major problem of cancer prevention practice or research, and the NCI is vigorously addressing this obstacle. Meeting the needs of special populations will require novel, effective and insightful measures, such as are being tested in the SELECT and other large NCI-supported chemoprevention trials. Complex risk-benefit and drug-interaction profiles (1, 3, 61, 76, 116–118) need to be worked out so that the results of positive cancer prevention trials can lead to standard prevention regimens for the groups most likely to benefit. The identification of these groups will require the development of molecular risk models and pharmacogenomic profiles. Innovative study designs and analysis methods are needed for translational trials that incorporate complex multiple biomarker end points (119). Important opportunities for cross-discipline development are therapeutic trials in cancer settings with a prevalence of early subclinical lesions. These trials should include nested prevention endpoints (*e.g.,* ACFs in colon cancer trials) when the study agents have preventive potential based on their mechanistic and safety profiles.

Disease prevention is a complex endeavor and outcomes models integrating multiple cancer and other clinical end points are needed to comprehensively assess promising cancer preventive agent classes, such as SERMs, 5α reductase inhibitors (5ARIs), PPARs, and NSAIDs, which can beneficially and adversely affect different diseases, including cancers and cardiovascular, inflammatory, brain, endocrine, and bone diseases. Future molecular studies of aging may find that atherogenesis, carcinogenesis, and other older age-related diseases share certain common molecular alterations that could be targeted by the same prevention approaches (120–126). The need to integrate prevention into the healthcare system is increasing, because it is predicted that without major advances in cancer prevention and treatment, growth and aging of the U.S. population will double the cancer burden in the next 50 years (127). The apparent efficacy of several agents (*e.g.,* folic acid, NSAIDs, calcium, and statins) against several common chronic diseases of aging (*e.g.,* cardiovascular disease, carcinogenesis, and neurodegenerative diseases) support this concept (128).

Many strong present foci and future visions of the science and practice of cancer prevention were presented during the AACR Frontiers meeting in Boston. These presentations highlighted the promising, innovative studies in chemoprevention, risk-reduction surgery, behavioral science and health services research, diet and nutrition, molecular genetics, epidemiology and imaging that have brought about a sea change in, and hold the keys to the future of, cancer prevention.

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Cancer Res 2003;63:5649-5655.