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Perspectives in Cancer Research

Cancer Prevention Science and Practice[1]

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A few decades ago, cardiology shifted research and treatment paradigms to absorb prevention as a major arm of its science and practice. Cardiology moved beyond exclusively treating major cardiovascular disease events (*e.g.,* acute myocardial infarction) to include identifying and treating risk factors (*e.g.,* with stents, statins, and lifestyle changes) to prevent first or second major events. Thus, cardiology set a precedent that oncology followed in expanding its paradigm to include cancer prevention. With some striking recent practical advances, cancer prevention has joined cancer therapy as a major, although less-established, approach for reducing cancer burden. This advance of cancer prevention came largely on the heels of the Phase III BCPT[3] of tamoxifen (1), which resulted in the first explicit FDA-approved and United States Preventive Services Task Force-recommended cancer risk reduction drug (2, 3); on a Phase IIb trial of celecoxib in FAP (4), which resulted in a high-profile cancer prevention-related FDA approval; and on the growing acceptance of certain cancer risk-reducing procedures such as fecal occult blood test, colonoscopic screening and polypectomy (5) or even prophylactic bilateral mastectomy (6) and oophorectomy (7). These recent high-profile practical advances of cancer prevention complement strong evolutionary advances in many areas of molecular prevention science such as mechanism-based drug development (8).

Molecular study indicates that carcinogenesis is multistep (accumulated genetic and epigenetic alterations; Refs. 9, 10), multipath (multiple functional pathways, *e.g.,* of apoptosis and angiogenesis; Refs. 11, 12), and multifocal (both multiclonal, *i.e.,* field cancerization, and clonal, *i.e.,* clonal expansion leading to intraepithelial spread; Refs. 13–16) and frequently is driven by genetic instability (15–17). Study of these processes helps to identify novel molecular targets for chemoprevention (8, 12, 14, 15, 18–20) and to guide the management of high-risk patients (21, 22), *e.g.,* by helping determine preventive drug efficacy (23) and surgical margin widths (14). A major challenge of cancer prevention is to integrate new molecular findings into clinical practice (14).

Molecular targeting research has brought about a revolution in drug development and is blurring the distinction between malignancy and premalignancy and between cancer therapy and prevention (2, 8, 12, 14, 15, 18–21, 24). Tamoxifen was developed first for cancer treatment (25) and later for prevention (1–3, 26). Indeed tamoxifen almost certainly both treated and prevented microscopic, subclinical disease in the BCPT (1, 2, 27), illustrating that therapy and prevention also are blurred at the clinical level [illustrated as well by SPT molecular studies and adjuvant/SPT prevention trials in the breast (2, 28, 29) and other sites (13, 30, 31)]. Now, drugs like cyclooxygenase 2 inhibitors cross from prevention (4, 15, 18, 19, 24) into therapy (32, 33), and molecular-targeting agents (*e.g.,* epidermal growth factor receptor inhibitors) can be developed for cancer therapy and prevention in the same Phase I study (34, 35). Notwithstanding its great potential and strides, molecular-targeting study still has a long way to go in clarifying the precise targets and effects of active agent classes, including complicated cross-target effects [*e.g.,* of NSAIDs (33, 36–40)] and effects on targets common to different sites [*e.g.,* the estrogen receptor, a target of breast (1, 2, 8, 18–20, 26, 28) and recently prostate (41) cancer prevention]. Major areas of molecular-targeting drug development include relevant new drug targets (*e.g.,* telomerase, HER2/neu, lipoxygenases, GATA-6, peroxisome proliferator-activated receptors, glutathione-*S*-transferase isoforms, activator protein-1, nuclear factor κB, Akt, phosphatidylinositol 3′-kinase, MAP kinase, glycogen synthase kinase 3β, cyclins, signal transducers and activators of transcription, matrix metalloproteinases, and vascular endothelial growth factor; Refs. 2, 8, 12, 14, 15, 18–20, 33, 36–38, 42–54), routes of administration (*e.g.,* oral, topical, intradermal, aerosolized; Refs. 19, 55–57), and approaches (*e.g.,* receptor tyrosine kinase inhibitors, chromatin modifiers, antisense, and gene targeting/therapy; Refs. 15, 19, 58–60). Prevention targets are being identified within UVA-, UVB-, fatty acid-, and tobacco-induced carcinogenesis (14, 15, 19, 36–40, 42, 43, 47, 52, 58). Target-specific cancer vaccines (57), *e.g.,* aimed at HER2/neu in breast carcinogenesis (61, 62), are being developed to improve on current nonspecific immunoprevention such as standard Bacillus Calmette-Guerin in superficial bladder tumors (63). Efforts also are under way to develop drugs targeting altered gene classes, functional signaling pathways (*e.g.,* of apoptosis), and genetic instability common to heterogeneous cancers and to develop chemoprevention combinations aimed at single or multiple molecular targets (2, 12, 14–19, 24, 32, 33, 36, 46, 50, 59). Combinations or agents with multiple targets should help in overcoming the serious problem of drug resistance due to the heterogeneous nature of carcinogenesis of different sites (64, 65) and within the same site (14, 15, 18, 19, 60, 66, 67).

Molecular and genetic epidemiology are tightly linked to surgical (6, 7, 68–70), behavioral (71, 72), and pharmacological (2, 4, 73, 74) prevention. Prophylactic resection of high-risk organs in certain germline mutation carriers is standard, albeit radical, prevention. For example, colectomy can reduce colorectal cancer risk in FAP patients, who have adenomatous polyposis coli mutations (4, 32), and bilateral mastectomy (6) and oophorectomy (7) can reduce breast cancer risk and breast and ovarian cancer risk, respectively, in BRCA mutation carriers. Prophylactic organ resections occasionally reveal occult IEN and/or cancer in the resected organ (70). The study of tamoxifen in individuals with germline BRCA2 mutation (74) and SULT1A1 polymorphisms, of finasteride in those with SRD5A2 polymorphisms (75), of retinoids in those with cyclin D1 polymorphisms (76), and of

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[3] The abbreviations used are: BCPT, Breast Cancer Prevention Trial; FDA, Food and Drug Administration; FAP, familial adenomatous polyposis; SPT, second primary tumor; NSAID, nonsteroidal anti-inflammatory drug; IEN, intraepithelial neoplasia; ATBC, Alpha-Tocopherol, Beta-Carotene; NCI, National Cancer Institute; DCIS, ductal carcinoma *in situ*; SELECT, Selenium and Vitamin E Cancer Prevention Trial; MMUS, minority and medically underserved.

NSAIDs in those with CYP2C9 and UGT1A6 genotypes (77) are important examples of the emerging field of preventive pharmacogenomics. Future directions should include developing new genetic susceptibility markers to better target IEN screening and prevention strategies in the young (5, 78), studying estrogen (79) and androgen (80) metabolism and targets (2, 19, 20, 41, 53), studying gene-environment and -nutrient interactions (15, 81, 82) and developing better biomarkers/models of exposure, risk, and preventive efficacy (14, 15, 19, 83, 84). Prevention research should increasingly integrate genomic studies with studies of environmental factors, lifestyle, and diet (84, 85).

Tobacco use is a major global problem causing many serious diseases (86–88), including cardiovascular disease and a growing list of cancers. The number of annual worldwide tobacco-related deaths is >4 million and is estimated by the World Health Organization to grow to 10 million (7 million in developing countries) by 2030 (86). In the United States, tobacco is the greatest preventable cause of morbidity and death and causes over $100 billion in economic costs each year (87). Intensive behavioral counseling (71, 89), pharmacological tobacco-dependence treatment (88), and legislative efforts to counteract tobacco advertising (87) and enhance quit rates have met with limited success in achieving durable smoking cessation (≥1 year). Two Phase III chemoprevention trials involving a total of 47,447 smokers, the ATBC Cancer Prevention Study (90) and β-Carotene and Retinol Efficacy Trial (91), found that β-carotene actually increased lung cancer incidence and mortality. A Phase III NCI retinoid trial to prevent SPTs associated with non-small cell lung cancer, the Lung Intergroup Trial (31), was neutral overall but found a provocative drug interaction with smoking status—potential harm in current smokers and benefit in never smokers with respect to lung cancer recurrence and mortality. In current smokers, Phase IIb trials have been generally negative (92, 93) but there are encouraging recent data (43, 94). Former smokers frequently have a high molecular risk of cancer (95), account for about half of all new United States lung cancers (96), and, as shown by the Lung Intergroup Trial (31) and recent Phase IIb studies (94, 97), are a promising population for lung cancer chemoprevention study. There also are promising chemoprevention results in the tobacco-related settings of head and neck (98–101) and bladder (63, 102) carcinogenesis. Improvement in tobacco-related cancer prevention approaches will require more scientific research on (*a*) genetic susceptibility to tobacco use (*e.g.*, involving variant D2 dopamine receptor genotypes; Refs. 103, 104); (*b*) the correlations between genotype/phenotype (23, 76) and surrogate/target tissue (105) in carcinogenesis and chemoprevention; (*c*) tobacco carcinogen metabolism (106) and interactions with important signaling pathways (107–109); and (*d*) risk in former tobacco users (95, 96) and people exposed to environmental tobacco smoke (106).

The biology and pharmacological and surgical treatment of premalignancy, or IEN, and IEN screening are major areas of cancer prevention. The concept of standard IEN chemoprevention gained prominence with the 1999 FDA approval of celecoxib in treating FAP (4). Two nearly simultaneous events in 2002, the publication of the AACR Task Force report on IEN endpoints for chemoprevention trials (110) and a landmark FDA Gastrointestinal Drugs Advisory Committee meeting on criteria for preventive drug trials in colorectal sporadic adenomatous polyps[4] (proposed criteria included duration of 3 years; treatment effect of 30% adenoma reduction; sample size of 1500 subjects) promise to greatly accelerate IEN chemoprevention study. Potentially, the FDA Gastrointestinal IEN meeting will have an impact on cancer prevention similar to the impact of a landmark 1981 FDA meeting on heart disease prevention. The 1981 meeting led to the rapid development and approval of drugs (*e.g.*, statins) based on serum lipid reductions (111). Many years later, lipid-reducing drugs produced profound reductions in major cardiovascular events (112, 113). Cardiovascular disease risk reduction strategies now include aggressive approaches such as drug-eluting stents (114). Not only may IEN treatment potentially reduce cancer risk but it also potentially can improve IEN symptoms, reduce screening intensity and frequency, and improve quality of life (110). Standard IEN screening, *e.g.*, Pap smear for cervical IEN, colonoscopy for adenomas, and mammography for DCIS, is part of cancer prevention and can lead to pharmacological, behavioral, or surgical interventions (5, 56, 68, 110, 115–117). New IENs are being identified, characterized, and integrated into prevention study and practice (65, 118). The future of IEN detection and risk assessment in clinical prevention includes identifying molecular pathologies in exfoliated cells (14, 119, 120), new sampling methods [*e.g.*, nipple aspirate and ductal lavage (15)] and novel imaging technologies (115, 121, 122). For example, human papilloma virus testing can enhance cervical screening (56), and testing for somatic mutations in stool (120) may greatly enhance fecal occult blood test screening (123). A major challenge of this work is to integrate screening and pharmacological approaches (2, 110, 123).

Although less developed than other standard preventive approaches, such as folic acid to prevent fetal neural tube defects during pregnancy, drinking water fluoridation to prevent dental caries, and statins to prevent heart disease, cancer chemoprevention has advanced greatly since important early animal prevention studies many decades ago (124, 125) and the first NCI clinical chemoprevention workshop ~20 years ago (126). This advance is documented in the AACR's 1999 Working Group (127) and 2002 IEN Task Force (110) reports and has contributed substantially to the maturation of cancer prevention in general. Clinical retinoid trials in treating IEN and preventing SPTs in the skin and head and neck provided chemoprevention's proof of principle (15, 18, 19, 98–101, 127–129). Tamoxifen later extended this proof into definitive risk reduction, producing from 30–50% reductions (*versus* placebo or nontamoxifen controls) in the risks of DCIS and primary or contralateral breast cancer (although only in estrogen receptor-positive disease) in a variety of important trials: the BCPT and International Breast Cancer Intervention Study in >20,000 high-risk women; National Surgical Adjuvant Breast and Bowel Project B24 Trial in >1,800 DCIS patients; and a series of adjuvant trials in >30,000 early breast cancer patients (1, 2, 26, 28, 29, 116). These results led to FDA approvals of tamoxifen in three distinct breast cancer risk reduction settings (2). Sulindac and celecoxib can effectively treat (but not prevent) adenomas in FAP (4, 130–132), high-dose celecoxib (800 mg/day) producing reductions of 28% in large bowel (4) and 14% in difficult-to-resect duodenal polyposis (*versus* placebo; Ref. 132). Aspirin (80 mg/day; Ref. 133) and calcium (1200 mg/day; Ref. 134) have achieved 19% and 15% overall reductions (*versus* placebo), respectively, in the risk of sporadic adenomas, with the greatest effect in later-stage disease (133, 135). Several other standard regimens, including hepatitis B vaccine to reduce the risk of liver cancer (136), Bacillus Calmette-Guerin and valrubicin to treat bladder IEN (Ta) and topical 5-fluorouracil, masoprocol, aminolaevulinic acid (with photodynamic therapy) and the NSAID diclofenate for treating actinic keratosis, also are cancer chemoprevention (15, 19, 63, 110), although they generally are not perceived as such. These regimens (along with several surgical risk reduction interventions also not usually considered cancer prevention) arise from IEN research, which is a cornerstone of cancer prevention research and practice (15, 18, 19, 110).

Despite its substantial progress and promise (18, 19), chemoprevention still faces many problems. There are the failures of lung

[4] Internet address: www.fda.gov/ohrms/dockets/ac/cder02.htm#Gastrointestinal>Drug.

cancer chemoprevention in smokers discussed earlier (19, 31, 90–93, 127). Some agents are preventive in one organ and carcinogenic in another, either clinically [*e.g.,* tamoxifen is preventive in the breast, carcinogenic in the uterus (1–3, 26, 137)] or in animal studies (*e.g.*, fenretinide is preventive in the breast and bladder but carcinogenic in the esophagus; Refs. 2, 127, 128, 138, 139). Some agents can be preventive and carcinogenic in the same organ, depending on different conditions/exposures (*e.g.*, different carcinogens or tumor promoters) in animals (127, 128, 138) or humans (31). There also are complex tradeoffs between cancer preventive agents' beneficial effects and their major noncancer adverse effects and interactions with other drugs in certain settings [*e.g.,* α-tocopherol-increased risk of hemorrhagic stroke in hypertensive smokers (90), tamoxifen-increased risk of pulmonary embolism (1, 2), effects of selective retinoid-X-receptor ligands, which are promising for breast cancer prevention (2), on thyrotropin secretion (140), and antioxidant interactions with lipid-altering agents (141)]. These problems highlight the profound complexity of carcinogenesis and preventive agent effects, the critical role for scientific research in addressing this complexity, and the need for stronger scientific rationales for clinical intervention (especially Phase III) trials, *e.g.,* from mechanistic and translational/IEN studies (2, 18, 19, 127, 138, 142).

Classical epidemiology is an important cancer prevention discipline that identifies populations at cancer risk and potential interventions to reduce this risk, which are important in generating hypotheses for controlled clinical trials (19, 127). Cancer epidemiology has provided important NSAID-colorectal-cancer data, which have been confirmed in randomized controlled trials (4, 110, 130, 132, 133), and important public health data on oral contraceptives (*e.g.,* regarding ovarian and breast cancer; Refs. 73, 143) and vasectomy (regarding prostate cancer; Ref. 144), which are unlikely to undergo randomized cancer prevention testing. Apparent benefit in these settings is not always confirmed in Phase III hypothesis testing trials, as was shockingly illustrated by β-carotene in the ATBC and β-Carotene and Retinol Efficacy Trial (90, 91) and hormone replacement therapy in the Heart and Estrogen/progestin Replacement Study and Follow-up and Women's Health Initiative (145). Epidemiological evidence (and secondary Phase III evidence to be discussed below) should have strong biological plausibility before testing as primary endpoints of costly, large-scale Phase III trials (2, 19, 127). The epidemiology of diet and nutrition established a link between dietary factors and cancer prevention that led to testing low-fat, high-fiber, and high-fruit and -vegetable diets in recent randomized sporadic adenoma trials (146–148). These trials underscore the evolution of this field, although they did not show reduced adenoma rates in the short term. Preclinical assessments of caloric restriction and dietary and nutritional factors and interactions in cancer development or prevention also are advancing the field (149–154). Several natural agents [*e.g.,* green and black teas (138, 149), isothiocyanates (150), curcumin (138, 151), and resveratrol (152)] and natural agent derivatives and synthetic analogues, including protease inhibitors (54, 153, 154), triterpenoids (155), and selenium and tocopherol compounds [*e.g.,* in prostate cancer (156, 157)] are under active preclinical study. Green tea's development from epidemiological to preclinical (138, 149) to Phase I (158) to ongoing Phase II testing is a recent example of rational drug development before any potential Phase III trial (159).

Secondary analyses of Phase III trials are another valuable source of hypothesis-generating evidence for new trials [*e.g.,* raloxifene in the Multiple Outcomes of Raloxifene; Evaluation (160) led to the Study of Tamoxifen and Raloxifene; anastrozole in the Arimidex and Tamoxifen Alone or in Combination trial (29) led to the International Breast Cancer Intervention Study 2; vitamin E in the ATBC (90) and selenium in the Nutritional Prevention of Cancer Study (161) led to the SELECT], providing perhaps the next highest level of evidence after Phase III primary endpoint data (2, 19). Secondary Phase III analyses also can generate complex risk-benefit (1–3, 19) and drug interaction (31, 141) profiles. Well-designed large Phase III trials [*e.g.,* NCI breast (BCPT, Study of Tamoxifen and Raloxifene), prostate (Prostate Cancer Prevention Trial, SELECT), and head and neck trials] offer valuable opportunities to conduct secondary/ancillary studies of basic mechanisms of disease development and drug effects, *e.g.,* via molecular and genetic epidemiological studies (2, 19, 74, 162, 163).

MMUS issues are a critical area of cancer prevention. Researchers must determine the relative impacts of biologic (*e.g.,* genetic susceptibility) and other (*e.g.,* low socioeconomic status, lifestyle choices, and access to medical care) factors on cancer risk and mortality in minority populations (2, 104, 142, 164–168). Low participation by MMUS populations is a persistent problem in cancer prevention practice or research (far greater than in cancer therapy), limiting the generalizability of cancer risk assessments (*e.g.,* the Gail breast cancer risk model) and risk-benefit profiles of preventive agents (2, 167, 168). This problem is being addressed vigorously by NCI-supported clinical trials such as the SELECT, which is using novel, effective measures to increase MMUS participation.[5]

Many other important prevention areas also need additional development. These areas include trial designs; statistical/outcomes models (to assess risk, surrogate endpoint biomarkers, and multiple cancer and noncancer endpoints; Refs. 19, 169); quality-of-life (170, 171), psychosocial (72), and cost-effectiveness (168) ancillary studies; bioinformatic strategies to analyze large amounts of data (*e.g.,* generated by cDNA microarrays; Ref. 172); the modeling, perception, and communication of risk (71, 72, 167, 168); prevention practice guidelines (3, 5); medical school and pre- and postdoctoral cancer prevention training programs; youth education programs on physical activity, sun exposure, diet, and tobacco use; research funding; legislative and public health policies (86, 87, 173); health insurance policies (159); barriers to prevention (*e.g.,* to IEN screening; Ref. 123); preventive drug accelerated approval (110) and patent life; processing and communicating data and information via computers and the internet (142); new approaches to prevent and treat infections that cause cancer (56, 66, 150, 174); preventive approaches and models for nonepithelial malignancies (174–176); and preclinical prevention model development (*e.g.,* tissue-specific, temporally regulated transgenic and knockout models; Refs. 176–180).

Cancer prevention has evolved and matured substantially in recent years. Certainly it has outgrown longstanding, imprecise definitions that include early detection of asymptomatic cancer and symptom control, rehabilitation, or other issues involved with cancer (181, 182). Advances in prevention science suggest that a better definition would include primary or second primary cancer risk reduction and IEN risk reduction or treatment. Prevention progress is reflected by the evolution in the NCI cancer prevention program over the past 30 years (126, 142, 159) and by the forefront role of cancer centers and the traditionally treatment-oriented United States national cooperative trials groups in clinical and translational prevention studies. Important steps toward formalizing prevention science and practice include activities of AACR in sponsoring the Working Group and IEN Task Force meetings and reports (110, 127) discussed earlier and most recently in launching a unique annual prevention meeting[6] focused on a comprehensive agenda of prevention disciplines. Public, academic, government, and industry acceptance of cancer prevention science as a major

[5] E. D. Cook, personal communication.

[6] This AACR conference is entitled Frontiers in Cancer Prevention Research: Genetics, Risk Modeling, Molecular Targets for Chemoprevention, Behavioral Prevention Research, Clinical Prevention Trials, Science and Public Policy and will take place in Boston, MA, October 14–18, 2002.

oncological specialty is increasing. This acceptance and the AACR's signal activities are helping to catalyze coordinated, focused, multidisciplinary research efforts that promise to accelerate the future contributions of cancer prevention to science and the public health. Even if cancer prevention progressed to the point of achieving vast reductions in the incidences of major cancers, as vaccines have done for many serious childhood diseases, a large role for oncology would be preserved in practicing the many, varied, and specialized prevention approaches for managing cancer risk and preinvasive disease.

The need for effective cancer prevention is growing (142, 183–185) based on predictions that growth and aging of the United States population will double the cancer burden in the next 50 years unless cancer prevention and treatment improve substantially (186). An exciting future vision for cancer prevention is to coordinate with prevention efforts in other diseases to reduce the burden of aging-related diseases. Carcinogenesis, atherogenesis, neurodegeneration, and other diseases commonly associated with aging have certain molecular alterations in common (18, 187–203). Emerging NSAID (33, 36, 52, 159, 190), selective estrogen receptor modulator (2, 26, 160, 191), peroxisome proliferator-activated receptor (45, 46, 192, 193), statin (112, 113, 194–197), cardiac-glycoside (198), and other data suggest that it may be possible to prevent or delay a spectrum of these diseases (15, 159, 201–203) with a single multitargeted regimen.

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