# Unprecedented Opportunities and Promise for Cancer Prevention Research

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## Abstract

Cancer prevention encompasses a wide range of highly developed science and clinical impact. Enunciating these two aspects in the same breath highlights the crucial link between them. The breadth and excitement of current opportunities in the science of cancer prevention have never been greater. Major avenues of such research include the extent and effect of premalignancy, the molecular underpinnings of carcinogenesis and related prevention targets, *in vitro* model systems of the progression of normal human epithelial cells to tumorigenesis, molecular risk stratification and pharmacogenomic approaches, and many more. We describe the clinical impacts of cancer prevention (with examples in the areas of molecular targeting, vaccines, epidemiology, and behavioral science) and the stage-setting science that facilitated them. In addition, discussed are new prevention opportunities such as interactions between stromal and microenvironmental factors, the control of premalignant stem cell phenotypes through epigenetic reprogramming, and neoplastic cells and various stress responses including those involving telomere biology. The promise of this science, particularly integrative, interdisciplinary research, is to hasten the ability of clinical prevention to reduce the burden of cancer. *Cancer Prev Res; 3(4); 394–402. ©2010 AACR.*

## Introduction

That cancer exacts an enormous toll on the world population has been recognized for a long time. So great is the direct and collateral damage of this disease to the U.S. population that former U.S. President Richard Nixon declared a "war on cancer," which led to the National Cancer Act of 1971 supporting research to provide a greater understanding of this enemy and better weapons for combating it. The ensuing decades of research have provided astonishing amounts of information on the molecular alterations that underlie different cancers and inform potential new avenues for their control.

Perhaps the most potentially far-reaching information to emerge from these studies points to cancer prevention as the most efficient way of waging this war. Why would prevention be more efficient than therapy? In aggregate, cancer studies have described in great depth and detail the derailment of cellular security systems and signaling gone awry, which is coupled with the daunting ability of tumor cells to mutate and evade therapeutic agents. Again

and again, cancer cells can evade chemotherapeutic agents and generate drug-resistant variants that progress to kill the patient. Yet, before cells transform to the point of needing chemotherapy, they likely exist in states that are much more amenable to interventions that control their future directions. New research efforts are identifying the factors that control these future directions and open the opportunity for modulating the context and outcome with respect to cancer development. Thus, these new insights suggest that prevention of cancer is a rational and ultimately effective method for dealing with this set of diseases.

It is useful here to define the range of concepts and approaches encompassed by the term "cancer prevention." Several steps within carcinogenic initiation and progression are appropriate targets for cancer prevention, which may take place at primary and secondary levels as described in detail below. *Primary prevention* is the avoidance of exposure to carcinogens or carcinogenic processes and frequently is directed at the population as a whole or at a rather broadly defined population. Although this area of prevention, for example through dietary changes or exercise, is perhaps most associated with the term cancer prevention among people not working in or very familiar with the field, it is important to remember that cancer prevention is not limited to this category. Examples of primary prevention are avoidance of tobacco smoke and psychosocial stress, chemically blocking exposure to pervasive environmental carcinogens such as aflatoxin, and induction of phase 1 or 2 enzymes to alter carcinogen metabolism. Another important area of primary prevention is natural agent chemoprevention in people with no signs of premalignancy (an approach that may be most effective in nutrient-deficient

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populations). *Secondary prevention* includes screening for and early detection of premalignancy or early, subclinical cancer and intervention to prevent progression to invasive disease or symptomatic cancer. Secondary prevention aims to eliminate or reduce existing risk in a generally more-defined, more-specified risk population (compared with primary prevention). The broad spectrum of secondary prevention comprises molecular high-risk settings (not necessarily including premalignant lesions) such as germline *BRCA* mutation carriers (e.g., prophylactic mastectomy) and colorectal adenomas [e.g., polypectomy, nonsteroidal anti-inflammatory drugs (NSAIDs)]. Last, *tertiary prevention* has been defined as preventing or controlling the symptoms and morbidity of cancer or the morbidity of cancer therapy (e.g., controlling pain with morphine or nausea with Compazine) and further as preventing recurrence or second primary cancer (e.g., with molecular-targeted chemoprevention) in patients after successful definitive treatment of early-stage cancer. These definitions of primary, secondary, and tertiary prevention conform conceptually with a gradient of cancer risk from normal or low, through moderate or high, to risk realized in established cancer.

In general contrast to participation in tertiary prevention or cancer therapy, enthusiasm for primary or secondary cancer prevention can be problematic. Presumptively healthy and disease-free (cancer or premalignancy) individuals sometimes are the least excited or motivated to participate in preventive interventions because the condition has not yet occurred (although in some ways this is an artificial boundary because current research indicates that premalignant lesions are common in people with no symptoms or diagnosis of disease). Most familiar to the public in the area of primary prevention are the recommendations to limit alcohol intake, food consumption, and stress conditions. These recommendations also assert positive effects from eating the proper foods and nutrients and obtaining adequate physical exercise. Although promulgated for a considerable length of time, these recommendations are still minimally effective in changing behavior, perhaps in part for lack of mechanistic understanding. New promise for primary cancer prevention, however, is developing out of behavioral linked with molecular science, for example, in the area of obesity and overweight, energy balance, and caloric restriction. Recent science has discovered the molecular basis, particularly actions of AMP-activated protein kinase and Akt pathways, of energy-balance effects, and caloric restriction is the most consistently positive approach for preventing cancer in animals. The overall study of controlling obesity and overweight to reduce cancer risk built on earlier work by Tannenbaum (1–3) and others in caloric restriction and the effects of various nutrients on animal model carcinogenesis.

The absence of invasive disease also can impede enthusiasm for secondary prevention, which can involve the impediment of invasive procedures (e.g., biopsy) to monitor and measure chemopreventive effects (e.g., in women with breast premalignancy) or the impediment of adverse drug effects that raise the omission bias, or the tendency to do nothing, although this avoids a lesser harm (e.g., a small increased risk of endometrial cancer with tamoxifen), rather than do something, although doing something would bring a greater benefit (e.g., a 50% reduced risk of breast cancer with tamoxifen).

Notwithstanding the aforementioned problems with participation in primary prevention, participation in primary prevention trials of natural agents such as vitamins, minerals, and antioxidants has been strong [e.g., 35,533 men randomized in the Selenium and Vitamin E (prostate) Cancer Prevention Trial]. This area of prevention, however, has encountered disappointing clinical results thus far. A recent blow was the very large, negative-neutral Selenium and Vitamin E Cancer Prevention Trial (4), which also is turning out to be a phoenix for natural agent prevention. The clinical ashes of the Selenium and Vitamin E Cancer Prevention Trial have stimulated tremendous interest in the science behind natural agents, such as pharmacogenomics, for improving their clinical batting average. For example, pharmacogenomic studies have shown that polymorphisms of manganese superoxide dismutase (*SOD2*) and *SEP15* (5) may identify men more likely to benefit from selenium for prostate cancer prevention, thus improving the overall prospects of natural agents for producing future clinical impact.

A critical concept underlying cancer prevention, as well as cardiovascular disease prevention, is that risk and pre–definitive end point conditions are diseases. Cardiology considers high cholesterol and atherogenesis to be diseases, and treating them with statins and aspirin is akin to primary and secondary cancer prevention. As it happens, there also is substantial interest in aspirin and statins [not to mention selective estrogen receptor modulators (SERMs) and vaccines] for cancer prevention, which highlights the cross-discipline aspects of many aging-related diseases including cardiovascular and neurodegenerative diseases, osteoporosis, macular degeneration, and cancer.

## New Conceptual Targets for Prevention

New molecular information suggests that powerful prevention efforts may come at the level of secondary prevention in the setting of premalignant lesions. Accumulating evidence suggests that premalignant lesions may be more common than previously appreciated. Studies by several investigators have shown a surprising prevalence of undetected premalignant lesions in "disease-free" individuals. Breast tissue provides a dramatic example of this phenomenon. For example, in one study of double mastectomy specimens from medicolegal autopsies, in which the cause of death was unrelated to breast cancer, nearly one-third (32%) harbored hyperplastic lesions, over one-quarter (27%) contained atypical ductal hyperplasia, almost one-fifth (18%) showed ductal carcinoma *in situ*, and 2% had invasive breast cancer (6). Furthermore, almost half of the women with ductal carcinoma *in situ* had bilateral

(41%) and/or multifocal (45%) disease. Another study of breast samples from random autopsies confirmed this high prevalence of undetected premalignant breast lesions (7). Similar data have been collected from examinations of prostate, bladder, pancreatic, lung, and colon tissue. These data indicate that the initiation of premalignant lesions, identified by morphologic alterations within the tissue, is by no means a rare event. This abundance of undetected or subclinical premalignant lesions compels us to ask why some premalignant lesions progress to cancer and others do not, a crucial question for cancer preventive interventions.

## New Opportunities in Prevention

### Stromal involvement in transitions from normalcy to malignancy

At least part of the answer to the foregoing question probably lies in the interactions between tumor epithelial cells and their stromal neighbors and the extracellular microenvironment. It is well known that stromal components undergo dramatic changes as a premalignant lesion or cancer progresses (8, 9). When and how these changes occur are under intense study. Stromal changes extend beyond the increase in endothelial cells for angiogenic support of tumor cells and beyond the influx of immune cells into the immediate tumor environment. Previous studies have shown that fibroblasts in the vicinity of a cancer, precancer, or inflammatory lesions express altered protein profiles such as increased growth factor and matrix metalloproteinase production (10). Previous studies in both an *in vivo* recombinant model and an *in vitro* coculture system have further shown that these fibroblasts can act in a functional manner to facilitate the transition to tumorigenicity in an otherwise nontumorigenic cell (11). These effects are not detected when normal fibroblasts and epithelial cells from the same human tissue specimen are grown under the same experimental conditions as the cancer-associated cells. Given these powerful effects of stromal components, the opportunity to modulate the signals and influence disease progression in these tissues is a new area for cancer prevention. These leading-edge stromal studies add to earlier and recent studies of the microenvironment and targeting angiogenesis and inflammation (12–14).

### Various stress responses and other opportunities

Recent work from several different directions is indicating a causal relationship between physiologic stress and alteration of molecular markers associated with cancer phenotypes. A differentiated cell's typical response to stress (physical, chemical, or physiologic) is to activate an arrest, senescent, or death response. Only cells that have sustained alterations can bypass this stress response and continue proliferating to form a premalignant or malignant lesion. Recent work has shown that the risk of future tumor formation is low in association with tissue biopsies exhibiting the activation of a stress response and high in association with tissue biopsies exhibiting a bypass of the stress arrest. These stress-related markers are proving to be useful in stratification of risk and will aid in targeting prevention efforts.

Adult somatic stem cells are exempt from this activation of stress-induced arrest processes. Programmed to respond to stress in a different manner than described above, these cells are recruited to sites of stress, stimulated to proliferate and reprogram cell fate, and positioned to reconstitute the injured or stressed tissue site. It has been hypothesized that these properties of adult somatic stem cells may qualify them as candidates for premalignant progression, for generating a group of cells with a minimal number of mutations but that manifest several premalignant properties. Because much of the control of stem cell phenotypes depends on epigenetic reprogramming, epigenetics has become a very promising area of basic and preclinical molecular-targeted prevention science. An important preclinical study of epigenetics showed that reversing methylation can prevent intestinal neoplasia in mice (15). Current epigenetic science is focused on risk markers and developing more selective and less toxic targeting agents. Research in this area also may shed light on the target cells for malignant transformation and novel opportunities for prevention (16).

Other areas of "stress" that are potentially applicable to advancing the science of cancer prevention involve telomere biology. To put this in context first, telomerase hyperactivity has been associated with malignant cells themselves in a wide range of human cancers. But conversely, telomerase in normal cells seems to be protective against cancer development through its ability to sustain telomere maintenance and, hence, genomic stability (17). As early as 2001, studies in rare inherited genetic diseases resulting in telomerase insufficiencies revealed that compromised telomere maintenance over a person's lifetime causes increased cancer risks in humans (18–20). In broader populations without genetic telomerase diseases, several studies show that telomere shortness is associated with major cancer risk factors including smoking, inflammation, and obesity (21). For example, studies have linked shortness of telomeres (and by implication, compromised telomere maintenance), which was measured in white blood cells, to the risk of Barrett's esophagus progressing to esophageal carcinoma (22) and to the risk of gastric cancer (23). Such findings in humans mirror similar conclusions drawn from various mouse-model studies (17).

Interesting findings indicate that a different type of stress, chronic psychological stress, takes its toll on telomere maintenance in humans (24, 25). This common type of stress has been extensively linked to increased risks of cardiovascular diseases and diabetes and other metabolic syndromes, and there are intriguing potential links between this nongenetic life factor and cancer that merit systematic exploration. Behavioral stresses, such as produced by social isolation, have been elucidated as factors in

cancer development and burden in recent animal studies (26, 27). A feeling of loneliness and hypervigilance may be important contributors to racial health disparities, specifically for breast cancer (28). Therefore, the intersection of telomere biology with the biology and behavioral science of stress provides a good example of how integrative, interdisciplinary science can contribute to cancer prevention approaches.

A model for how telomere maintenance could be usefully applied clinically in cancer prevention may be drawn from cardiovascular disease prevention. A West of Scotland study (29) of statins for preventing cardiovascular disease in people with one or more cardiovascular risk factors (but not symptoms of disease) provides an example (and biomarker) with potential relevance to cancer prevention. This study showed that individuals with shorter telomere length in white blood cells at the study outset were selectively protected from future heart disease by statin treatment. Because the statin-associated benefit occurred only in individuals with shorter telomeres, this biomarker not only preidentified the group with sensitivity to clinically beneficial statin effects but also showed potential for use in sparing nonsensitive individuals from the inherent risks associated with taking statins. Scientific advances in telomere biology similarly promise to have implications for cancer prevention, including behavioral/pharmacologic interventions, the development of molecular risk models, and molecular-targeted chemoprevention approaches (e.g., targeting regulation of telomerase).

## New Molecular Insights: Risk Stratification

Although sophisticated imaging techniques are increasing the ability to detect premalignant lesions (30), the majority of these preinvasive lesions are not associated with future tumor formation (31). Over the last four decades, investigators have tried extensively to identify clinicopathologic variables and molecular markers that may be important in predicting which premalignancy patients will progress to invasive cancer. Identification of such variables would help to prevent overtreatment (thus reducing morbidity) and undertreatment (thus reducing mortality). Several recognized lesion variables are routinely assessed in the clinic (e.g., size, nuclear grade, and surgical margins) and some have been found to have predictive value for subsequent in situ but not invasive disease. However, none have proven strong enough to fully support choices for intervention (hazard ratios of from approximately 2–5) and none have predicted a future invasive event. Although focused on associating risk with the differential expression of molecular markers, more recent studies also have found no molecular features that can distinguish between premalignant lesions that do and do not precede a tumor event. Because of the lack of distinguishing markers, current clinical practice offers all individuals diagnosed with premalignant lesions the same treatment options, from complete organ (breast or prostate) removal to "watchful

waiting." Because most premalignant lesions are not associated with subsequent invasive tumors, it is likely that many individuals diagnosed with in situ disease will be overtreated. Conversely, because even with this therapy some initially observed in situ lesions are followed by subsequent invasive carcinomas, some individuals with in situ disease may be undertreated. New approaches to identify true malignant precursors with high sensitivity and specificity are desperately needed and are being developed (31, 32).

Other current science in this area is modeling germline and somatic markers of risk and predictive markers (of agents' beneficial and toxic effects) toward personalizing cancer prevention (5, 33–38). These efforts are leading toward comprehensive, complex modeling in clinical cohorts that will depend on evolving statistical methodology, highlighting the crucial role of biostatistical researchers in developing new methods needed for studies of cancer prevention, detection, and treatment. There are many areas where biostatisticians are responding to new types of biological data and public-health concerns in developing the tools needed for study design, analysis, and interpretation, including, for example, the efficient design and analysis of studies to detect genetic associations with disease, efficient methods to detect subgroups that are particularly susceptible to an environmental exposure (or "gene-environment interaction"), methods to estimate and evaluate absolute disease risk, methods to integrate risk estimation with public-health decisions, and methods to use longitudinal biomarker data to understand evolving patterns of risk. Based on this science, clinical trials of various agents in highest risk people could be developed, early cancer detection could be enhanced, and prevention could be personalized to individuals sensitive to a particular agent and at the highest risk of cancer.

## Early Causal Events in Cancer and the Opportunity for Prevention

There are imposing barriers to the identification of early causal alterations in tumor cells. Because of these difficulties, many laboratories use tumor cells in culture that are derived from highly progressed metastatic lesions. Although these cells are useful for studying later steps in the transition to malignancy, they are inadequate for studying the early steps of carcinogenesis or primary or secondary prevention efforts. These tumor cells have already accumulated numerous gross, chromosomal abnormalities, as well as many molecular alterations, thus making it difficult to reconstruct the early events that lead to malignancy.

An alternative approach to identifying early causal events is to grow normal human epithelial cells in culture and then define conditions that would convert them to tumorigenicity. Hence, the development of in vitro model systems became a focused effort in the field. These models need to preserve the functional biology of transformation

and allow the examination of cells throughout the process of initiation and progression. Efforts from several laboratories over the past three decades have provided culture systems that allow for the isolation and propagation of normal human epithelial cells, for example from human breast tissue (39, 40), and allow investigators to examine the processes required for transformation. Some studies have treated breast cells with chemical carcinogens and obtained mutant mammary epithelial cells that are tumorigenic (41). Other laboratories have introduced viral carcinogens such as the SV40 large T antigen, in conjunction with other molecular alterations (e.g., activated ras and overexpression of telomerase), to obtain malignant cells (42). An alternative approach has been to identify a variant subpopulation of human epithelial cells that possess properties of premalignant lesions without any exposure of the cells to viral, chemical, or physical carcinogens (43). These variant cells exist *in vivo* and express markers often seen in tumors (44, 45).

A limitation of this approach is the scarcity of disease-free tissue. Recognizing this barrier, the U.S. National Cancer Institute is currently launching a program to procure human tissue at each stage of the disease continuum, starting with disease-free tissue and encompassing malignant tissues. This initiative should support novel, previously impossible prevention studies. Although surrogate studies in murine cells and tissues have been educational about general principles of malignant transformation, critical details of cellular signaling are not conserved between mouse and human tissues. Therefore, human tissue is needed.

## Cancer Prevention Science and Clinical Impact

A rich stream of scientific discovery has informed past clinical advances and impact of cancer prevention. Presented in the following paragraphs, a few of these many exciting, leading scientific channels are loosely grouped as molecular targeting, vaccines, and epidemiology and behavioral science.

### Molecular targeting

Molecular targeting involving sex hormones has produced major clinical advances. The SERMs tamoxifen and raloxifene reduced preinvasive and/or invasive ER-positive breast cancer risk by ~50% in women with a higher-than-average risk (46, 47). This overall reduction comprised a far higher reduction (69%) in ER-positive disease, consistent with tamoxifen effects in premalignancy (atypical hyperplasia, ductal carcinoma *in situ*), adjuvant therapy (contralateral second primary cancers and recurrence), and advanced cancer therapy (48). Long-term (post–primary report) follow-up within the large primary prevention trials of these SERMs highlights the important role that such extended analyses can have in strengthening and/or modifying the interpretation of primary findings. The major science underlying these clinical impacts included work of Lathrop and Loeb in the early 1900s (49) showing that castration (oophorectomy)

in female mice reduced mammary tumor incidence, follow-on clinical studies of oophorectomy in genetically high-risk women (50–52), and the discovery of the ER in 1966 (53) and tamoxifen prevention of mammary tumors in rats in 1974 (54). There also have been clinical advances with large prevention trials of the 5-α-reductase inhibitors finasteride and dutasteride (55–57) that sprang from work of Huggins (58) in the 1940s showing that castration benefitted patients with metastatic prostate cancer and subsequent study of androgen metabolism and signaling. The current science in hormonal prevention is working to develop newer and better SERMs and other approaches for interfering with estrogen metabolism, such as with aromatase inhibitors for reducing ER-positive breast cancer risk. New approaches for the much-needed prevention of ER-negative breast cancer include targeting HER1/2 signaling.

Clinical trials have established the preventive activity of cyclooxygenase-2 (COX-2)–specific inhibitors and other NSAIDs in familial adenomatous polyposis (59) and sporadic colorectal adenomas (60, 61) and show that the NSAID aspirin may reduce colorectal cancer risk (62). These clinical advances built on studies showing that colorectal screening and polypectomy can reduce colorectal cancer by 90% (63), epidemiology showing consistent NSAID associations with reduced colorectal adenoma and cancer risk and mortality, and work of the mid-1990s showing COX-2 upregulation in human colorectal adenomas (64) and that COX-2 targeting was effective in APC-knockout mice (65). Current scientific research involving the signaling pathways targeted by these agents includes work on germline and somatic molecular predictors of NSAID activity (66–68), work on COX-2 regulation and downstream and related targets (69, 70), and work to elucidate the molecular risk factors involved in the highly publicized adverse cardiovascular effects of COX-2 inhibitors (71), which have essentially stopped interest in these agents for clinical cancer prevention. The problem of unexpected serious adverse effects also has limited public acceptance of the other highly active targeted agents tamoxifen for breast cancer prevention (largely because of an increased risk of endometrial cancer; ref. 72) and finasteride for prostate cancer prevention (largely because of an apparently increased risk of high-grade prostate cancer; ref. 56).

A major clinical trial of combined difluoromethylornithine and the NSAID sulindac (73) prevented colorectal adenomas/polyps and is one approach that began to address the issue of adverse events associated with molecular-targeted cancer prevention. This trial built on and validated earlier concepts of combination chemoprevention (74) and built on the science behind COX-2/NSAIDs cited above. The promise of this approach is synergistic or additive preventive effects when the agents are combined, which allows the lowest active dose of each agent and thus lowers the potential for adverse effects. The toxicity of molecular-targeted prevention is being addressed by other approaches as well, including more selective agents (e.g., raloxifene, which has a lower

endometrial neoplasia risk than does tamoxifen; ref. 47), local delivery (e.g., intravesical rapamycin; ref. 75), and intermittent, short-term regimens (e.g., with tumor antigen vaccines or other approaches in colorectal cancer prevention; refs. 76, 77).

## Vaccines

One of the most successful approaches for preventing disease, vaccines prevent ~6 million annual deaths worldwide. The science of vaccines is one of the most promising areas of ongoing cancer prevention research. Clinical studies established the efficacy of hepatitis B virus (HBV) vaccination of children in preventing hepatocellular cancer in Taiwan (78, 79). The science driving this clinical advance included Blumberg's discovery of HBV in 1967 (80) and its link with hepatocellular carcinoma (81). clinical trials established that human papillomavirus (HPV) vaccines reduced the risks of cervical, vulvar, and vaginal neoplasia (82, 83), and HPV screening has led to major advances in early detection and surgical prevention of cervical cancer (84). These vaccines generate mainly antibody (type II) responses and were effective primarily before and not after HPV exposure. These clinical impacts were driven by zur Hausen's work (85) showing the link between HPV and cervical cancer in 1974 and the discovery of the first specific human HPV (HPV-16) in cervical cancer patients (86). Recent studies have documented a causal link between HPV-16 and oropharyngeal carcinogenesis (87) and suggested that a well-established racial disparity in the outcome of oropharyngeal cancer treatment is related to a lower prevalence in blacks of HPV-positive oropharyngeal cancer, which responds better to therapy (88). The importance of this work is highlighted by an alarming recent increase in oropharyngeal cancer incidence in the United States and other countries, which has important implications for HPV vaccines in this setting.

Another approach is endogenous tumor antigen vaccines (which induce a predominant type I cellular response), which is a burgeoning area of scientific research with potential applications to cancer prevention. This approach has been used in advanced cancer, unsuccessfully, but has shown recent promising results in the adjuvant setting or in minimal cancer and so may work in premalignancy/prevention settings. Current prevention science involving antitumor vaccines is studying HER2 (breast) and MUC1 (colon rectum) antigen vaccines in mice (77, 89, 90). An important potential advantage of cancer prevention vaccines is limited toxicity due to short-term dosing, which is being used with the antivirus vaccines and will be used with tumor antigen vaccines if, as planned, they can sustain a tumor antigen–specific immune response after only a few doses. Recent data indicate that a new type of HPV vaccine (eliciting a predominant type I cellular response) is active against HPV-associated vulvar intraepithelial neoplasia (91). Limited, short-term dosing regimens differentiate vaccines from other active chemopreventive agents such as tamoxifen or COX-2 inhibitors, which require long-term, daily dosing to achieve effect.

Defending against infection-related cancer includes approaches besides vaccination. For example, a clinical trial of combined antibiotics eradicated Helicobacter pylori in patients and reduced rates of new gastric cancer (92). This clinical advance was built on the 1984 science of Marshall and Warren showing the link of Helicobacter pylori with duodenal and gastric diseases (93). Although only 20% of current cancers are known to be infection-related, the portfolio of such cancers is growing (94). For example, the incidence of HPV-related oropharyngeal cancer is increasing dramatically (87) and a link between Merkel polyomavirus and Merkel cell carcinoma is emerging (95), highlighting the increasing importance of vaccines and other anti-infection approaches for preventing cancer.

### Epidemiology, behavioral science, and tobacco

Epidemiology, behavioral science, and public policy have produced a major clinical impact in reducing smoking rates. The first pharmacologic intervention for overcoming smoking dependence, the nicotine patch, was approved by the U.S. Food and Drug Administration in 1984. This clinical impact was founded on a profound body of scientific study of the relationship of tobacco and cancer. Key epidemiologic studies linking smoking to lung cancer were reported in 1950 (96, 97), and Auerbach (98) established the histopathologic link of smoking with bronchial epithelial changes in 1957, leading to important studies of tobacco carcinogens and molecular field effects including new molecular risk models, target discovery, and preventive agent development approaches (99–101). The addictive nature of smoking was established in the 1990s, including the important link of tobacco dependence with germline genetic variation (102). Current work in this area is focused on developing better pharmacologic means, including nicotine vaccines, for overcoming tobacco dependence (103).

The previous paragraphs describe examples of great science leading to great clinical impact. Not all science leads to clinical homeruns, however, and it is crucial that we accept some scientific dead ends in the overall quest to push back the frontiers of cancer prevention science (104). The not inconsiderable discovery of the Americas by 15th century Europeans, after all, began as a misguided effort to discover an oceanic trade route between Europe and the Indies.

## Conclusions

Cancer biology intersects with several areas and disciplines of cancer prevention, pointing to opportunities for and the importance of integrative, interdisciplinary efforts to advance clinical cancer prevention through hard-won science. Current studies are elucidating the extent and effect of premalignancy and the molecular underpinnings of carcinogenesis involving stromal interactions and epigenetic

and other alterations. The basic study of carcinogenesis for prevention also is advancing with the development of *in vitro* model systems of the progression of normal human epithelial cells to tumorigenesis. Molecular risk-stratification and pharmacogenomic approaches promise to identify the populations with the greatest need for, and the greatest potential to benefit from, clinical cancer prevention. Cancer prevention science and practice will gain from better educating and communicating to (*a*) the general research community about the mechanistic underpinnings of prevention advances such as linking obesity/overweight to cancer development and (*b*) everyone, especially at-risk populations and their primary care providers, about the overall benefits, sight of which can be lost in the face of adverse aspects, of clinical advances such as colorectal screening (which reduces colorectal neoplasia by up to 90%), and tamoxifen (which reduces breast cancer risk by 50%).

The clinical impact of cancer prevention in several areas, for example, molecular-targeted drugs in preventing various major cancers, vaccines in preventing virus-related cancers, and smoking control measures in reducing lung cancer risk, not only facilitates new science on the aforementioned and many more important fronts but also has highlighted the tremendous stage-setting science that preceded the impact. From epidemiologists to behavioral and basic scientists to clinical trialists to biostatisticians—every prevention discipline contributes key research to this science.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## References

1. Tannenbaum A. The genesis and growth of tumors. II. Effects of caloric restriction per se. Cancer Res 1943;3:749–56.
2. Hursting SD. Mechanistic insights into reducing the weight of breast cancer. Cancer Prev Res 2009;2:295–7.
3. Pollak M. Macronutrient intake and cancer: How does dietary restriction influence tumor growth and why should we care? Cancer Prev Res 2009;2:698–701.
4. Lippman SM, Klein EA, Goodman PJ, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the selenium and vitamin E cancer prevention trial (SELECT). JAMA 2009;301:39–51.
5. Penney KL, Schumacher FR, Li H, et al. A large prospective study of SEP15 genetic variation, interaction with plasma selenium levels, and prostate cancer risk and survival. Cancer Prev Res. In press, 2010.
6. Nielsen M, Thomsen JL, Primdahl S, Dyreborg U, Andersen JA. Breast cancer and atypia among young and middle-aged women: a study of 110 medicolegal autopsies. Br J Cancer 1987;56:814–9.
7. Alpers CE, Wellings SR. The prevalence of carcinoma in situ in normal and cancer-associated breasts. Hum Pathol 1985;16:796–807.
8. Tlsty TD, Coussens LM. Tumor stroma and regulation of cancer development. Annu Rev Pathol Mech Dis 2006;1:119–50.
9. Eng C, Leon G, Orloff MS, Ostrowski MC. Genomic alterations in tumor stroma. Cancer Res 2009;69:6759–64.
10. Ronnov-Jessen L, Petersen OW, Bissell MJ. Cellular changes involved in conversion of normal to malignant breast: importance of the stromal reaction. Physiol Rev 1996;76:69–125.
11. Olumi AF, Grossfeld GD, Hayward SW, Carroll PR, Tlsty TD, Cunha GR. Carcinoma-associated fibroblasts direct tumor progression of initiated human prostatic epithelium. Cancer Res 1999;59:5002–11.
12. Folkman J, Watson K, Ingber D, Hanahan D. Induction of angiogenesis during the transition from hyperplasia to neoplasia. Nature 1989;339:58–61.
13. Gandhi L, McNamara KL, Li D, Borgman CL, et al. Sunitinib prolongs survival in genetically engineered mouse models of multistep lung carcinogenesis. Cancer Prev Res 2009;2:330–7.
14. Wong K-K, Jacks T, Dranoff G. NF-κB fans the flames of lung carcinogenesis. Cancer Prev Res 2010;3:403–5.
15. Laird PW, Jackson-Grusby L, Fazeli A, et al. Suppression of intestinal neoplasia by DNA hypomethylation. Cell 1995;81:197–205.
16. Issa J-P. Cancer prevention: epigenetics steps up to the plate. Cancer Prev Res 2008;1:219–22.
17. Artandi SE, DePinho RA. Telomeres and telomerase in cancer. Carcinogenesis 2010;31:9–18.
18. Vulliamy T, Marrone A, Goldman F, et al. The RNA component of telomerase is mutated in autosomal dominant dyskeratosis congenita. Nature 2001;413:432–5.
19. Vulliamy TJ, Marrone A, Knight SW, Walne A, Mason PJ, Dokal I. Mutations in dyskeratosis congenita: their impact on telomere length and the diversity of clinical presentation. Blood 2006;107:2680–5.
20. Marrone A, Sokhal P, Walne A, et al. Functional characterization of novel telomerase RNA (TERC) mutations in patients with diverse clinical and pathological presentations. Haematologica 2007;92:1013–20.
21. Valdes AM, Andrew T, Gardner JP, et al. Obesity, cigarette smoking, and telomere length in women. Lancet 2005;366:662–4.
22. Risques RA, Vaughan TL, Li X, et al. Leukocyte telomere length predicts cancer risk in Barrett's esophagus. Cancer Epidemiol Biomarkers Prev 2007;16:2649–55.
23. Hou L, Savage SA, Blaser MJ, et al. Telomere length in peripheral leukocyte DNA and gastric cancer risk. Cancer Epidemiol Biomarkers Prev 2009;18:3103–9.
24. Epel ES, Blackburn EH, Lin J, et al. Accelerated telomere shortening in response to life stress. Proc Natl Acad Sci U S A 2004;101:17312–5.
25. Epel ES, Lin J, Wilhelm FH, et al. Cell aging in relation to stress arousal and cardiovascular disease risk factors. Psychoneuroendocrinology 2006;31:277–87.
26. Williams JB, Pang D, Delgado B, et al. Model of gene-environment interaction reveals altered mammary gland gene expression and increased tumor growth following social isolation. Cancer Prev Res 2009;2:850–61.
27. Hermes GL, Delgado B, Tretiakova M, et al. Social isolation dysregulates endocrine and behavioral stress while increasing malignant burden of spontaneous mammary tumors. Proc Natl Acad Sci U S A 2009;106:22393–8.
28. McClintock MK, Conzen SD, Gehlert S, Masi C, Olopade F. Mammary cancer and social interactions: identifying multiple environments that regulate gene expression throughout the life span. J Gerontol B Psychol Sci Soc Sci 2005;60:32–41.
29. Brouilette SW, Moore JS, McMahon AD, et al. Telomere length, risk of coronary heart disease, and statin treatment in the west of Scotland primary prevention study: a nested case-control study. Lancet 2007;369:107–14.

30. Roblyer D, Kurachi C, Stepanek V, et al. Objective detection and delineation of oral neoplasia using autofluorescence imaging. Cancer Prev Res 2009;2:423–31.

31. Gauthier ML, Berman HK, Miller CJ, et al. Abrogated stress response distinguishes basal-like tumors and DCIS lesions associated with subsequent tumor events. Cancer Cell 2007;12:479–91.

32. Berman HK, Gauthier ML, Tlsty TD. Premalignant breast neoplasia: a paradigm of inter- and intralesional molecular heterogeneity and its biological and clinical ramifications. Cancer Prev Res. In press, 2010.

33. Wacholder S, Hartge P, Prentice R, et al. Performance of common genetic variants in breast-cancer risk models. N Engl J Med 2010; 362:986–93.

34. Li Y, Sheu C-C, Ye Y, et al. GPC5 genetic variants are associated with lung cancer risk in never smokers. Lancet Oncol. In press, 2010.

35. Beane J, Sebastiani P, Whitfield TH, et al. A prediction model for lung cancer diagnosis that integrates genomic and clinical features. Cancer Prev Res 2008;1:56–64.

36. Varella-Garcia M, Schulte AP, Wolf HJ, et al. The detection of chromosomal aneusomy by fish in sputum predicts lung cancer incidence. Cancer Prev Res 2010;3:447–53.

37. Wu X, Spitz MR, Lee JJ, et al. Novel susceptibility loci for second primary tumors/recurrence in head and neck cancer patients: large-scale evaluation of genetic variants. Cancer Prev Res 2009;2:617–24.

38. Lipkin SM, Chao L, Moreno V, et al. Genetic variation in HMG-CoA reductase modifies the chemopreventive activity of statins for colorectal cancer. Cancer Prev Res. In press, 2010.

39. Hammond SL, Ham RG, Stampfer MR. Serum-free growth of human mammary epithelial cells: rapid clonal growth in defined medium and extended passage with pituitary extract. Proc Natl Acad Sci U S A 1984;81:5435–9.

40. Band V, Sager R. Distinctive traits of normal and tumor-derived human mammary epithelial cells expressed in a medium that supports long-term growth of both cell types. Proc Natl Acad Sci U S A 1989; 86:1249–53.

41. Walen KH, Stampfer MR. Chromosome analyses of human mammary epithelial cells at stages of chemical-induced transformation progression to immortality. Cancer Genet Cytogenet 1989;37:249–61.

42. Hahn WC, Counter CM, Lundberg AS, Beijersbergen RL, Brooks MW, Weinberg RA. Creation of human tumor cells with defined genetic elements. Nature 1999;400:464–68.

43. Romanov SR, Kozakiewicz BK, Holst CR, Stampfer MR, Haupt LM, Tlsty TD. Normal human mammary epithelial cells spontaneously escape senescence and acquire genomic changes. Nature 2001; 409:633–7.

44. Crawford YP, Gauthier M, Joubel A, et al. Histologically normal human mammary epithelia with silenced p16INK4a overexpress COX-2, promoting a premalignant program. Cancer Cell 2004;5:263–73.

45. Fordyce C, Fessenden T, Pickering C, et al. DNA damage drives an activin a-dependent induction of cyclooxygenase-2 in premalignant cells and lesions. Cancer Prev Res 2010;3:190–201.

46. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 1998;90: 1371–88.

47. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP study of tamoxifen and raloxifene (STAR) P-2 trial. JAMA 2006;295:2727–41.

48. Lippman SM, Brown PH. Tamoxifen prevention of breast cancer: an instance of the fingerpost. J Natl Cancer Inst 1999;91:1809–19.

49. Lathrop AE, Loeb L. Further investigations on the origin of tumors in mice. III. On the part played by internal secretion in the spontaneous development of tumors. J Cancer Res 1916;1:1–19.

50. Lynch HT, Harris RE, Organ CH, Jr., et al. The surgeon, genetics, and cancer control: the Cancer Family Syndrome. Ann Surg 1977; 185:435–40.

51. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med 2002;346:1616–22.

52. Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med 2006;354:261–9.

53. Toft D, Gorski J. A receptor molecule for estrogens: isolation from the rat uterus and preliminary characterization. Proc Natl Acad Sci U S A 1966;55:1574–81.

54. Jordan VC. Antitumour activity of the antioestrogen ICI 46,474 (tamoxifen) in the dimethylbenzanthracene (DMBA—induced rat mammary carcinoma model. J Steroid Biochem 1974;5:354.

55. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. N Engl J Med 2003;349:215–24.

56. Redman MW, Tangen CM, Goodman PJ, Lucia MS, Coltman CA, Jr., Thompson IM. Finasteride does not increase the risk of high-grade prostate cancer: a bias-adjusted modeling approach. Cancer Prev Res 2008;1:174–81.

57. Andriole GL, Pettaway CA, TC, ILF, Somerville MC. Incidence of biopsy-detectable prostate cancer in the REduction of DUtasteride of Prostate Cancer Events (REDUCE) trial: Blinded 2-year results (abstract #2207). Presented at the Annual Meeting of the American Urological Association, Chicago (IL). 2009.

58. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1941;1:293–7.

59. Steinbach G, Lynch PM, Phillips RK, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med 2000;342:1946–52.

60. Baron JA, Cole BF, Sandler RS, et al. A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med 2003;348:891–9.

61. Bertagnolli MM, Eagle CJ, Zauber AG, et al. Celecoxib for the prevention of sporadic colorectal adenomas. N Engl J Med 2006;355: 873–84.

62. Flossmann E, Rothwell PM. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. Lancet 2007;369:1603–13.

63. Winawer SJ, Zauber AG, Ho MN, et al, The National Polyp Study Workgroup. Prevention of colorectal cancer by colonoscopic polypectomy. N Engl J Med 1993;329:1977–81.

64. Eberhart CE, Coffey RJ, Radhika A, Giardiello FM, Ferrenbach S, DuBois RN. Up-regulation of cyclooxygenase 2 gene expression in human colorectal adenomas and adenocarcinomas. Gastroenterology 1994;107:1183–8.

65. Oshima M, Dinchuk JE, Kargman SL, et al. Suppression of intestinal polyposis in Apc δ716 knockout mice by inhibition of cyclooxygenase 2 (COX-2). Cell 1996;87:803–9.

66. Chan AT, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. N Engl J Med 2007;356: 2131–42.

67. Chan AT, Zauber AG, Hsu M, et al. Cytochrome P450 2C9 variants influence response to celecoxib for prevention of colorectal adenoma. Gastroenterology 2009;136:2127–36.

68. Martinez ME, O'Brien TG, Fultz KE, et al. Pronounced reduction in adenoma recurrence associated with aspirin use and a polymorphism in the ornithine decarboxylase gene. Proc Natl Acad Sci U S A 2003;100:7859–64.

69. Shureiqi I, Jiang W, Zuo X, et al. The 15-lipoxygenase-1 product 13-S-hydroxyoctadecadienoic acid down-regulates PPAR-δ to induce apoptosis in colorectal cancer cells. Proc Natl Acad Sci U S A 2003; 100:9968–73.

70. Holla VR, Backlund MG, Yang P, Newman RA, DuBois RN. Regulation of prostaglandin transporters in colorectal neoplasia. Cancer Prev Res 2008;1:93–9.

71. Duffield-Lillico AJ, Boyle JO, Zhou XK, et al. Levels of prostaglandin E metabolite and leukotriene E(4) are increased in the urine of smokers: evidence that celecoxib shunts arachidonic acid into the 5-lipoxygenase pathway. Cancer Prev Res 2009;2: 322–9.

72. Waters EA, Cronin KA, Graubard BI, Han PK, Freedman AN.

Prevalence of tamoxifen use for breast cancer chemoprevention among U.S. women. Cancer Epidemiol Biomarker Prev 2010;19: 443–6.

73. Meyskens FL, Jr., McLaren CE, Pelot D, et al. Difluoromethylornithine plus sulindac for the prevention of sporadic colorectal adenomas: a randomized placebo-controlled, double-blind trial. Cancer Prev Res 2008;1:32–8.

74. Sporn MB. Combination chemoprevention of cancer. Nature 1980; 287:107–8.

75. Seager CM, Puzio-Kuter AM, Patel T, et al. Intravesical delivery of rapamycin suppresses tumorigenesis in a mouse model of progressive bladder cancer. Cancer Prev Res 2009;2:1008–14.

76. Zhang Lf, Ren X, Alt E, et al. Chemoprevention of colorectal cancer by targeting APC-deficient cells for apoptosis. Nature. In press, 2010.

77. Weiner LM, Surana R, Murray J. Vaccine prevention of cancer: can endogenous antigens be targeted? Cancer Prev Res 2010;3:410–5.

78. Chang MH, Chen CJ, Lai MS, et al, Taiwan Childhood Hepatoma Study Group. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. N Engl J Med 1997;336:1855–9.

79. Chang MH, You SL, Chen CJ, et al. Decreased incidence of hepatocellular carcinoma in hepatitis B vaccinees: a 20-year follow-up study. J Natl Cancer Inst 2009;101:1348–55.

80. Blumberg BS, Gerstley BJ, Hungerford DA, London WT, Sutnick AI. A serum antigen (Australia antigen) in Down's syndrome, leukemia, and hepatitis. Ann Intern Med 1967;66:924–31.

81. Blumberg BS. Bioethical questions related to hepatitis B antigen. Am J Clin Pathol 1976;65:848–53.

82. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915–27.

83. Koutsky L. The epidemiology behind the HPV vaccine discovery. Ann Epidemiol 2009;19:239–44.

84. Schiffman M, Wacholder S. From India to the world-a better way to prevent cervical cancer. N Engl J Med 2009;360:1453–5.

85. zur Hausen H, Meinhof W, Scheiber W, Bornkamm GW. Attempts to detect virus-secific DNA in human tumors. I. Nucleic acid hybridizations with complementary RNA of human wart virus. Int J Cancer 1974;13:650–6.

86. Durst M, Gissmann L, Ikenberg H, zur Hausen H. A papillomavirus DNA from a cervical carcinoma and its prevalence in cancer biopsy samples from different geographic regions. Proc Natl Acad Sci U S A 1983;80:3812–5.

87. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. N Engl J Med 2007; 356:1944–56.

88. Settle K, Posner MR, Schumaker LM, et al. Racial survival disparity in head and neck cancer results from low prevalence of human papillomavirus infection in black oropharyngeal cancer patients. Cancer Prev Res 2009;2:776–81.

89. Disis ML. The ultimate in cancer chemoprevention: cancer vaccines. Cancer Prev Res 2010;3:406–9.

90. Beatty PL, Narayanan S, Gariépy J, Ranganathan S, Finn OJ. Vaccine against MUC1 antigen expressed in inflammatory bowel disease and cancer lessens colonic inflammation and prevents progression to colitis-associated colon cancer. Cancer Prev Res 2010;3:438–46.

91. Kenter GG, Welters MJP, Valentijn ARPM, et al. Vaccination against HPV-16 oncoproteins for vulvar intraepithelial neoplasia. N Engl J Med 2009;361:1838–47.

92. Fukase K, Kato M, Kikuchi S, et al. Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. Lancet 2008;372:392–7.

93. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1984;1:1311–5.

94. Blaser MJ. Understanding microbe-induced cancers. Cancer Prev Res 2008;1:15–20.

95. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science 2008;22:1096–100, 319.

96. Doll R, Hill AB. Smoking and carcinoma of the lung; preliminary report. Br Med J 1950;2:739–48.

97. Wynder EL, Graham EA. Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma; a study of 684 proved cases. J Am Med Assoc 1950;143:329–36.

98. Auerbach O, Forman JB, Gere JB, et al. Changes in the bronchial epithelium in relation to smoking and cancer of the lung;a report of progress. N Engl J Med 1957;256:97–104.

99. Spira A, Beane J, Shah V, et al. Effects of cigarette smoke on the human airway epithelial cell transcriptome. Proc Natl Acad Sci U S A 2004;101:10143–8.

100. Schembri F, Sridhar S, Perdomo C, et al. MicroRNAs as modulators of smoking-induced gene expression changes in human airway epithelium. Proc Natl Acad Sci U S A 2009;106:2319–24.

101. Boyle JO, Gümüş ZH, Kacker A, et al. Effects of cigarette smoke on the human oral mucosal transcriptome. Cancer Prev Res 2010;3: 266–78.

102. Carmelli D, Swan GE, Robinette D, Fabsitz R. Genetic influence on smoking-a study of male twins. N Engl J Med 1992;327:829–33.

103. Cerny EH, Cerny T. Vaccines against nicotine. Hum Vaccin 2009; 5:200–5.

104. Blackburn EH, Greider CW, Szostak JW. Telomeres and telomerase: the path from maize, Tetrahymena and yeast to human cancer and aging. Nat Med 2006;12:1133–8.