Do We Make Optimal Use of the Potential of Cancer Prevention?

1

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Abstract Three decades of intensive experimental and clinical research on cancer prevention have yielded an impressive body of scientific knowledge about cancer epidemiology, causation, and preventative measures. Despite our increased understanding in these critical areas, this knowledge is not being translated adequately into initiatives that will impact public health. The recent release of the World Cancer Research Fund/American Institute for Cancer Research report on diet and lifestyle strategies for cancer prevention—grounded in an evidence-based, systematic review of the published literature—is a strong acknowledgment of the benefits of a lifestyle approach to reduce cancer risk. The report also emphasizes the need to increase basic nutritional science research to make optimal use of the knowledge gained in the past three decades. Medical approaches—represented by chemoprevention clinical trials—also have become more focused based on results from basic science leads. The expansion of preclinical chemoprevention studies and greater attention to "first-in-human" prevention trials that safely shorten the timeline for new drug development are needed. The development of a prevention focus for what the U.S. Food and Drug Administration calls "exploratory investigational new drug studies" and what investigators at the National Cancer Institute are calling "phase 0" clinical trials will contribute to the decision-making involved in designing larger cancer prevention clinical trials. Past achievements in phase III prevention clinical trials—such as the Prostate Cancer Prevention Trial, the Breast Cancer Prevention Trial, and the Study of Tamoxifen and Raloxifene—have provided early successes as evidence of the potential for public benefit to be derived from this research. Nevertheless, the application of these findings to clinical practice and the design of future prevention trials remains a challenge. Current strategies include the refinement of risk assessment models for several major cancers. Additional initiatives, based on emerging basic and clinical research, involve the development of potential biomarkers for cancer risk and early detection by the National Cancer Institute's Early Detection Research Network. Although a recent progress report indicates that biomarkers of cancer susceptibility and exposure have been identified, continued work is needed to validate such markers for clinical use. Using this information optimally for prevention through lifestyle changes or medical interventions will

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demand commitments from public and private research institutions. Another area of emerging research is the development of a systems biology approach to cancer prevention. This will demand the creation of multidisciplinary teams of researchers from biological sciences, informatics and engineering scientists, and researchers from many fields not generally focused on disease prevention. To facilitate this and other new approaches, and to make effective use of information and strategies for cancer prevention, intensive training efforts must be implemented to develop the next generation of basic and clinical scientists—and physician researchers—capable of working in a cross- and multidisciplinary research environment. Training current researchers in new approaches will add efficiency to their combined research experiences.

1.1 Introduction

For most of the past 35 years, trends in the incidence and mortality rates of all major cancers in the United States showed steady increases. This pattern changed in the 1990s when decreases started to emerge (National Cancer Institute 2007), with mortality rates declining at approximately half that of incidence rates (Ries et al. 2007). While for some of the most common types of cancer in the United States—breast, prostate, colorectal, and lung—considerable progress has been made regarding mortality and incidence, in specific cancer types in some population groups (e.g., lung cancer in women and prostate cancer among African Americans) such progress is not evident.

The role of cancer prevention underlies much of this observed decrease in cancer incidence and mortality. For three decades, an impressive body of research has accumulated indicating that lifestyle and medical prevention strategies can have a major impact on cancer incidence and mortality. Nevertheless, doubt exists as to whether clinicians and other health professionals are making optimal use of existing knowledge regarding cancer prevention strategies. Cancer prevention offers a key opportunity to reduce the disease burden both on individuals and on the healthcare system. To achieve the maximum benefit from cancer reduction, major initiatives in prevention must include both lifestyle and chemoprevention approaches.

The following sections discuss current research on lifestyle and medical intervention studies—as well as selected molecular and genetic studies—in cancer prevention. In addition, a review is presented of progress in several areas: the translation of research findings into public benefit; new approaches for designing and developing clinical trials to target individuals most likely to benefit from trial findings; and suggestions for increased and novel approaches to training with a goal of producing the multidisciplinary researchers needed for working with emerging high-throughput and "-omic" (e.g., genomic, proteomic, transcriptomic, and metabolomic) technologies.

1.2 Lifestyle Interventions

Preventing cancer through lifestyle modifications and other interventions has received increased attention in the past decade as more is understood about the role of nutrition, weight gain/loss, and the level of physical activity and cancer risk. Since the Doll and Peto quantitative analysis of estimates of avoidable cancer risks in 1981 (Doll and Peto 1981), accumulating evidence suggests that lifestyle may contribute to as much as 70% of cancer cases; nutrition alone is a factor in at least 30%–40% of cancers. Adopting lifestyle modifications—in areas involving diet,

physical activity, use of tobacco, and weight control—offers a major approach to cancer prevention for most individuals. In the past, however, apart from the avoidance of tobacco, limited convincing evidence had been available to make recommendations regarding these lifestyle areas. This situation changed rapidly as findings from basic, epidemiological, and clinical research began to fill in gaps in our knowledge. For example, the recent release of *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective* (World Cancer Research Fund 2007)—the 2007 expert report developed and published by the World Cancer Research Fund (WCRF) and the American Institute of Cancer Research (AICR)—highlighted the role of lifestyle on cancer prevention. The report is evidence-based and draws from a substantial body of cancer prevention literature published in the past decade.

What distinguishes this recent report from past documents is the utilization of increasingly available data from controlled clinical trials and large prospective studies on nutrition and cancer. Table 1.1 highlights the recommendations from the report, which incorporates government recommendations (U.S. Department of Health and Human Services 2005). Table 1.2 highlights the report's findings on lifestyle factors and decreased or increased risk of cancer by cancer site. The inclusion of a factor in Table 1.2 indicates that the authors of the report found the evidence to be either "probable" or "convincing" for its use in assessing the level of cancer risk. "Convincing" is the highest level of evidence for a recommendation, based on the judgment that the evidence will be unlikely to change over time and is based on congruent results from at least two independent cohorts. The underlying evidence has favorable attributes including: (1) no substantial heterogeneity in the data; (2) plausible dose responses; (3) consistent evidence from laboratory studies; and (4) accountability for error. Taken in totality, the evidence suggests that specific lifestyle changes could have a major impact on cancer prevention if optimal use of the information became part of physician practice and public policy recommendations.

Table 1.1 WCRF/AICR (2007) recommendations adapted from *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*, incorporating 2005 U.S. dietary guidelines

General recommendations for cancer prevention
1. Be as lean as possible without becoming underweight (goal: BMI 21–23)
2. Be physically active for at least 30 min every day
3. Avoid sugary drinks. Limit consumption of energy-dense foods (particularly processed foods high in added sugar, or low in fiber, or high in fat)
4. Eat more of a variety of vegetables, fruits, whole grains and legumes such as beans
5. Limit consumption of red meats (such as beef, pork, and lamb) and avoid processed meats
6. If consumed at all, limit alcoholic drinks to 2 for men and 1 for women a day
7. Limit consumption of salty foods and foods processed with salt (sodium). Avoid moldy cereals (grains) or legumes
8. Aim to meet nutritional needs through diet alone. Do not use supplements to protect against cancer
Special population recommendations
9. New mothers ideally should breastfeed exclusively for up to 6 months and then add other liquids and foods
10. Cancer survivors after treatment should follow the recommendations for cancer prevention

Table 1.2 Convincing evidence of decreased or increased risk of cancer by cancer site and lifestyle factor (*Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*; WCRF/AICR 2007)

Lifestyle factors with probable and/or convincing decreased risk of cancer[a]	
Colorectum	Foods containing dietary fiber, garlic, milk, calcium supplements, increased physical activity (probable evidence)
Mouth, pharynx, larynx	Non-starchy vegetables, fruits, foods containing carotenoids (probable evidence)
Esophagus	Non-starchy vegetables, fruits, foods containing beta-carotene (probable evidence)
Stomach	Non-starchy vegetables, *Allium* vegetables, fruits (probable evidence)
Lung	Fruits, foods containing carotenoids (probable evidence)
Pancreas	Foods containing folate (probable evidence)
Prostate	Foods containing lycopene, foods containing selenium, selenium supplements (probable evidence)
Breast	Lactation
Lifestyle factors with probable and convincing increased risk of cancer[a]	
Liver	Aflatoxins
Colorectum	Red meat, processed meat, alcoholic drinks (men only), body fatness, abdominal fatness, adult-attained height
Lung	Arsenic in drinking water, beta-carotene supplements
Mouth, pharynx, larynx	Alcoholic drinks
Esophagus	Alcoholic drinks, body fatness
Breast, premenopausal	Alcoholic drinks (probable evidence)
Breast, post-menopausal	Alcoholic drinks, body fatness, adult-attained height
Pancreas	Body fatness
Endometrial	Body fatness
Kidney	Body fatness

[a] Evidence is convincing unless otherwise noted as probable

The potential for research opportunities geared toward improving the science of nutrition and cancer emerged directly from this report. These opportunities include integrating the recommendations on chronic diseases, and on promoting positive health and well-being. The relationship between causation and prevention should be elucidated and a revived look at descriptive studies, such as those on migrant populations, is needed.

Other important research gaps include studies on determinants of rapid growth and early puberty; dietary energy restriction in humans; food systems and dietary patterns; foods common in traditional diets; populations in parts of the world for which cancer is uncommon; and follow-up studies of exclusively breastfed children. There also is a need to develop standard definitions of physical activity and processed meat, and to determine when in the course of life specific preventative interventions are most effective. WCRF and AICR have committed to regularly updating the report as new evidence is published. (A summary and complete report can be found at http://www.wcrf.org/research/fnatpoc.lasso.)

Other important findings of the past decade relating lifestyle interventions to cancer prevention include the emerging recognition of obesity as a major factor in cancer etiology. Calle and

colleagues suggested that being overweight or obese contributes to 15%–20% of cancer deaths; given the increasing numbers of obese Americans, the promotion of weight control has potential as a broadly effective lifestyle approach to cancer prevention (Calle et al. 2003). Regular, moderate physical activity also has been associated with reduced risk of various cancers, including colon cancer (Samad et al. 2005).

A preventative approach of lifestyle modifications that targets diet, physical activity, and weight control is likely to impact morbidity and mortality due to cancer.

1.3 Medical Interventions

Unlike lifestyle interventions, which are generally designed to target cancer risk broadly in populations, medical interventions are more specific in that they focus on limited cancer types in individuals or subpopulation groups that are at increased risk of developing those cancers. Both types of intervention, however, are important for overall reductions in cancer morbidity and mortality. The field of study involving the medical intervention approach to cancer prevention is maturing as it incorporates knowledge generated from basic, epidemiological, and clinical research. In particular, the increased understanding of the molecular, genetic, and epigenetic processes that contribute to or prevent carcinogenesis feeds directly into the formulation of medical preventative interventions. New approaches for designing and implementing cancer prevention clinical trials will also directly affect investigators' ability to provide evidence of benefits (or lack of benefit) for medical interventions. The use of emerging technologies and the collaborative efforts of multidisciplinary research teams are expected to accelerate the pace of new discoveries.

1.4 The Changing Landscape of Clinical Studies

The use of lifestyle or medical interventions ideally depends on their evaluation in clinical trials—preferably testing each intervention in relation to a control group in a randomized controlled trial (RCT). Before cancer prevention agents—nutrient- and non-nutrient-based—can be tested in RCTs, however, they must undergo testing in a phased clinical trial regimen to guarantee the safety and efficacy of the agent. For cancer prevention clinical research, the U.S. National Cancer Institute (NCI) traditionally has used a three-phase approach for testing chemoprevention agents. These potential chemoprevention agents are tested for safety and pharmacokinetic profiles in a small number of individuals (phase I trial); intermediate-endpoint biomarkers that are modulated by the agent and have potential to serve as surrogates for clinical disease endpoints are identified and tracked in trials with as many as several hundred individuals (phase II trial or a combination of phase I and phase II trials); and a large-scale, randomized, controlled trial is conducted to determine if the agent reduces cancer risk, the critical clinical endpoint in cancer prevention research (phase III trial). NCI encourages extensive follow-up to further evaluate the long-term safety and efficacy of an intervention. More than 150 potential chemopreventative agents have been identified in preclinical studies sponsored by the NCI's Division of Cancer Prevention (DCP), and development continues on the more than 40 agents that have shown evidence of safety and chemopreventative efficacy. Figure 1.1 depicts the approach of chemoprevention research and the stages in the carcinogenic process that may be targeted by chemopreventative agents.

An effort is being made at NCI to shorten the time an agent spends in the phased system, and

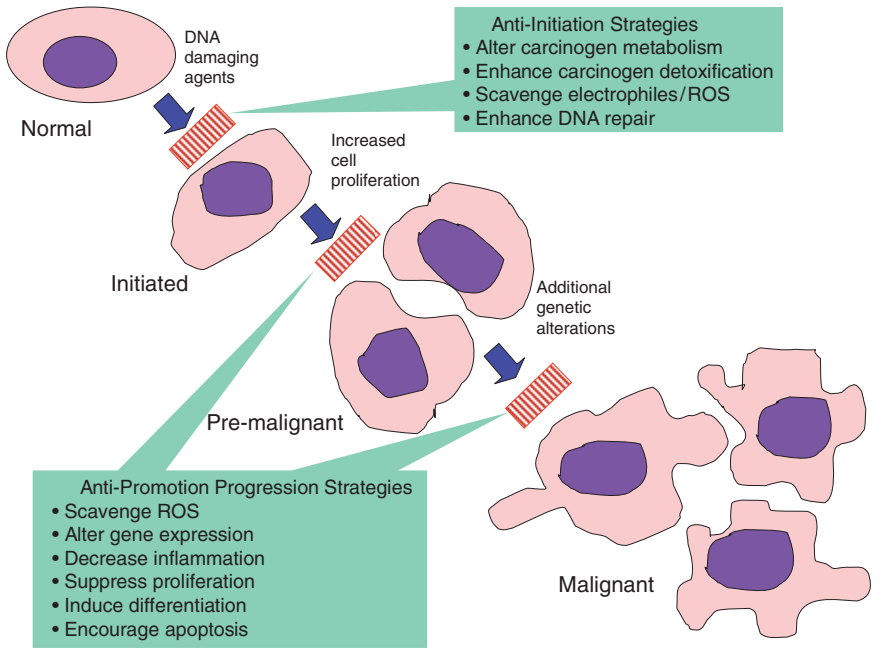

Fig. 1.1 Chemoprevention strategies in the carcinogenic process. (Adapted from Greenwald 2002, reproduced with permission from the BMJ Publishing Group)

to reduce the number of agents in need of testing in phase I and phase II trials prior to advancing to a more definitive, higher phase of clinical testing. In the past, one of the shortcomings of the phased system has been its inability to eliminate early in the process those agents that make their way to phase II trials but are deemed inappropriate for phase III trials because of unsatisfactory results from the phase II trials (e.g., lack of efficacy or safety). The recent implementation of "phase 0" trials makes use of advances in methodologies and technologies to study the pharmacokinetic and pharmacodynamic properties of an agent before introduction to the traditional phased system. Pharmacokinetic studies address the movement, distribution, and fate of an agent in the body over time. Pharmacodynamic testing, in contrast, elucidates the biochemical and physiological effects of an agent on the body, focusing on the drug's interaction with various molecular and cellular structures within target tissues. Considered together, data from pharmacokinetic and pharmacodynamic studies help researchers determine a rational dosage regimen for testing in the conventional phases (I, II, III) of clinical trials. A phase 0 trial utilizes much lower doses of drug, thereby minimizing risk, in fewer patients. This approach allows agents that are not producing the desired effects to be weeded out earlier, and in this manner may shorten by up to a year the time it takes to move a potential chemopreventative agent from the laboratory to actual clinical use.

New genomic, proteomic, and metabolomic investigational techniques, together with novel high-throughput and imaging technologies are having an impact on the time it takes for new chemopreventative agents (and drugs for disease treatment) to move from the laboratory to the clinic. The U.S. Food and Drug Administration (FDA) has developed the Critical Path Initiative for agent (drug) development that is meant to

speed the process used for moving promising agents forward to clinical development (Green 2007). The initiative was developed based on the observation that fewer investigational new drug (IND) applications were being submitted in the past few years. Thus, the Critical Path Initiative was developed to study the tools and strategies for "proof-of-principle" studies or, as they are sometimes known, "first-in-human" studies; these tools and strategies are critical for determining whether development of specific agents should move forward. In addition, the time and cost of moving to "first-in-human" studies is reduced. The FDA is optimistic that the Critical Path Initiative will improve the efficiency of the drug-testing process and encourage researchers, both private and public, to increase their commitment to the development of new agents for the prevention and treatment of cancer as well as other chronic diseases.

1.5 Prevention Clinical Trials

Clinical prevention trials have shown that specific agents can reduce the risk of different cancer types. Making optimal use of this evidence for clinical practice is critical for reducing the burden of cancer on society. Examples of clinical trials with impressive results for cancer prevention, with major potential for translation into clinical practice, are those for breast and prostate cancers. In addition, large screening trials are currently being conducted for prostate, colon, lung, and ovarian cancers, with the intent of evaluating modalities for early detection, allowing more effective clinical management and thereby reducing the resulting cancer burden.

The Prostate Cancer Prevention Trial (PCPT) was the first large-scale phase III trial for prevention of prostate cancer. PCPT tested the 5-alpha-reductase inhibitor finasteride, which inhibits the conversion of testosterone to dihydrotestosterone, a key promoter of prostate cancer. This placebo-controlled trial of 7 years duration included more than 18,000 men with normal digital rectal examination (DRE) and serum prostate-specific antigen (PSA) less than 3 ng/ml. In 2003, the PCPT findings showed that finasteride reduced the period prevalence of prostate cancer by approximately 25% compared with placebo (Thompson et al. 2003). Participants in the finasteride group who did develop prostate cancer, however, had a higher incidence of high-grade tumors, in the range of Gleason score 7–10, than those in the placebo arm. The concern precipitated by this observation led to a re-analysis of the PCPT data on high-grade tumors (Lucia et al. 2007). Results of the re-analysis suggested that the increase in high-grade cancer was due, at least in part, to increased detection. This, in turn, resulted from the normal part of the prostate having volumes that were lower in the finasteride than the placebo group, thus selectively facilitating detection of any cancerous tissue nested in prostate exposed to drug. Such detection bias appears to have been more important than any direct effects of the intervention on tumor morphology. As a result, high-grade cancer was detected at earlier stages and was less extensive in the finasteride group than in the placebo group.

Clinical trials addressing breast cancer prevention have yielded adequate knowledge to improve prevention efforts in the public arena. One of the best examples from three decades of clinical experience with breast cancer prevention is the knowledge gained from the Breast Cancer Prevention Trial (BCPT) together with that from subsequent trials. The BCPT began recruiting in 1992 for premenopausal and postmenopausal women at an increased risk of developing breast cancer. More than 13,300 women were accrued to the trial and randomized to a tamoxifen or placebo arm. Results of the trial indicated that women taking tamoxifen had 49% fewer diagnoses of invasive breast cancer and noninvasive breast cancer (e.g., ductal or

lobular carcinoma in situ) compared to women in the placebo arm of the trial (Fisher et al. 1998). Concerns, however, were raised in the BCPT about the increase in endometrial cancer and thromboembolic events among women taking tamoxifen. In search of an equally or more effective preventative agent that would be less toxic, the Study of Tamoxifen and Raloxifene (STAR) compared raloxifene, an approved osteoporosis drug, to the BCPT-established standard of care for breast cancer prevention, tamoxifen. Results of STAR indicated that raloxifene was as effective as tamoxifen in reducing the risk of invasive breast cancer, but did not increase the risk of endometrial cancer and thus had a better overall benefit:risk profile (Vogel et al. 2006).

Many challenges exist for reducing the incidence of breast cancer, especially in those cancers that are not hormonally mediated. Additional agents are being investigated for preventative efficacy in preclinical and clinical studies in selected populations; these include aromatase inhibitors, retinoids, and bioactive food components (BFCs; e.g., soy and fish oil). The roles of timing of exposure, dose, and presence of other risk factors are only now beginning to be understood. This is especially true for nutritional approaches to cancer prevention. Research on soy and breast cancer illuminates the complexity of the effects of dietary factors on cancer risk. Several epidemiological studies have suggested that higher intake of soy or soy products is associated with a reduction in breast cancer risk, at least in some populations (Wu et al. 1998). For certain women, however, soy appears to increase the risk of breast cancer, which suggests that soy may be a dietary factor that can be both beneficial and harmful, depending on the circumstances. Because isoflavones preferentially bind to and activate the estrogen receptor (ER) and have estrogen-like properties, this activity has been proposed as the mechanism by which soy isoflavones reduce the risk of ER+ breast cancer (Messina et al. 2006). In contrast, further in vitro and animal studies, and a few small human studies, indicate that soy isoflavones (i.e., genistein) can stimulate the growth of pre-existing ER+ tumors. More studies are planned to investigate whether timing of intake of soy or soy products has an impact on breast cancer risk in high-risk women or on survival of breast cancer patients. Polymorphisms in genes relevant to estrogen metabolism and activity also appear to have both positive and negative effects on breast cancer risk through the modulation of soy isoflavones. The negative correlation between breast cancer risk and urinary and serum isoflavone levels was especially strong for women with a particular polymorphism in the gene *ESR1*, which encodes the estrogen receptor, the critical mediator of signaling in cells in response to estrogen (Low et al. 2005a). For women with the variant ESR1 genotype, differences in mean plasma estradiol levels for the highest and lowest tertiles of serum isoflavones would translate into a more than 30% difference in breast cancer risk.

A similar situation occurs with soy and prostate cancer. Isoflavones may modulate circulating androgen and estrogen concentrations in men and affect the risk of prostate cancer, which, like breast cancer, may be hormone dependent. The soy metabolites enterolactone and equol affect plasma androgen concentrations, and this may be modified by *CYP19A1* (cytochrome P450, family 19, subfamily A, polypeptide 1) polymorphisms (Low et al. 2005b). Case-control studies have found that men with the ability to degrade the soybean isoflavone, daidzein, to equol have a lower incidence of prostate cancer than men lacking this ability (Akaza et al. 2004).

Screening trials evaluate interventions aimed at the early detection of pre-cancer and/or cancer, in the hope that this approach will translate into a decreased cancer burden. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, for example, is a large-scale clinical trial designed to determine whether certain cancer screening tests reduce deaths from prostate, lung, colorectal, and ovarian cancer. The premise of the trial is that cancers identified at earlier

stages lend themselves to more effective treatments. PLCO also is important because it is targeting four cancers that cumulatively account for approximately 42% of new cancers each year in the United States as well as 46% of deaths.

PLCO began accruing participants in 1992 and in 2001 completed the randomization into two study groups: (1) the comparison group comprising participants who receive routine healthcare from their health providers, and (2) the intervention group comprising participants who receive a series of designated, scheduled exams to screen for prostate, lung, colorectal, and ovarian cancers. The screening of participants ended in 2006, with follow-up exams to continue for up to 10 years to determine the benefits or harms of screening. Preliminary findings on follow-up testing for men with unusual DRE or PSA levels higher than 4.0 ng/ml have shown that 74.2% of men with positive screening tests underwent additional diagnostic testing; 31.5% underwent biopsy, with 1.4% of the men in the screening arm diagnosed with prostate cancer (Andriole et al. 2005). Similar compliance and follow-up testing was seen among participants undergoing screening for the other PLCO cancers. Whether enhanced compliance to screening will lead to reductions in mortality from these four cancers will not be known until well past 2010.

1.6 Biomarkers for Cancer Prevention

A major challenge for prevention clinical trials has been securing timely endpoints to provide adequate proof that cancer (or other chronic disease) has been prevented. This often takes a decade or more in cancer prevention clinical trials, as participants must be followed long enough for disease rates to be examined. Such long trial durations, compounded by the need for participant sample sizes large enough to achieve adequate event rates for statistical evaluation, can stress the limited resources available for cancer-related research. In an age when methodological, computational, and technological advances evolve in vastly shorter periods of time, cancer prevention researchers have begun looking for biomarkers to serve as surrogate markers to identify cancer risk, assist in early detection and progression of disease, and to assess the efficacy of preventative (i.e., lifestyle or medical) interventions. Measurement of biomarkers can provide empirical evidence of the effect of interventions in basic research or clinical trials by identifying their impact on molecular and cellular pathways related to disease initiation and progression. In addition, surrogate endpoint biomarkers (SEBs) offer the promise of reducing the time needed to determine if cancer prevention interventions have a benefit (or cause harm). However, at present, putative SEBs still have to be validated in the context of clinical trials.

Biomarkers can serve multiple purposes in clinical research; they may be used for early detection as well as to determine susceptibility, exposure, or effect of an intervention. For example, in cancer prevention clinical trials using lifestyle interventions, biomarkers of exposure to dietary factors are commonly assessed to document exposure and determine cancer risk (Milner 2003). The advent of emerging technological and methodological approaches in nutrition science has made possible more accurate measurements of dietary intakes and metabolic processes involved in interactions that may influence cancer risk. For example, basic research on dietary isothiocyanates (ITCs), found primarily in cruciferous vegetables, has elucidated mechanisms-of-action that suggest a role for these nutrients in preventing carcinogenesis. These mechanisms include inhibition of carcinogen-activating enzymes, induction of carcinogen-detoxifying enzymes, increase of apoptosis, and arrest of cell cycle progression (Zhang 2004). Preclinical and human studies have provided evidence that the intake of ITCs is inversely related to the risk of lung, breast, and colon cancers (Zhang 2004). Because ITCs are

metabolized and excreted in urine, their usefulness as a biomarker of exposure has been hypothesized and confirmed in clinical studies.

To address the need for identifying cancer prevention biomarkers, in 2000 the National Cancer Institute established the Early Detection Research Network (EDRN), an investigator-driven network designed to conduct translational research aimed at identifying biomarkers both for the early detection of cancer and for documentation of cancer risk (National Cancer Institute 2008). EDRN investigators have more than 120 biomarkers in development and have been instrumental in identifying and initiating validation studies of markers for major cancers, such as: prostate (protein profiling of serum for high-grade prostatic intraepithelial neoplasia and levels of PCA3, a noncoding RNA, in urine); colon (*K-ras* mutations in stool and urine); and breast (panels of autoantibodies in sera). Clinical validation studies are in progress for serum colon cancer-specific antigen (CCSA)-2 and CCSA-3 in colon cancer and serum des-gamma-carboxy prothrombin and alpha-fetoprotein-L3 in liver cancer. A signature accomplishment of the EDRN is its development of a process to validate biomarkers; validation confers the highest level of confidence that the biomarker is linked to the disease process and provides a "proof-of-principle" of its use in risk assessment, diagnosis, and/or treatment. EDRN is collaborating with investigators from large clinical studies to obtain biologic samples for use in validating specific biomarkers. Biomarkers that were validated in several of these preliminary studies will subsequently be tested in sera from cases and matched controls collected in the PLCO trial.

Samples from the PLCO trial also have been made available to biomarker investigators based on an application process open to all. For example, a recent biomarker study investigated the relationship of obesity-related hyperinsulinemia to increased risk of prostate cancer, a previously suggested association (Weiss et al. 2007). Insulin-like growth factor (IGF)-1 and IGF binding protein (IGFBP)-3 have been shown from experimental studies to influence cellular growth, metabolism, and apoptosis, with potential impacts on prostate cancer. A nested case-control study was conducted from prediagnostic serum samples collected for the PLCO trial; 727 incident cases of prostate cancer and 887 matched controls were assessed for levels of IGF-1 and IGFBP-3. Results of the study showed no overall association between IGF-1 and IGFBP-3 (independently) and prostate cancer risk. However, the molar ratio of IGF and IGFBP-3 was related to the risk for aggressive prostate cancer in obese men (Weiss et al. 2007). The design of the PLCO trial allowed the collection of samples at baseline and each year during the trial, up to the year cancer was diagnosed. This sample repository is a valuable resource that may be shared with investigators who are seeking to identify, develop, or validate biomarkers of risk or for early detection.

For making optimal use of our increasing knowledge of biomarkers in cancer prevention, there must be increased planning for collection of biomarker information in prevention clinical trials. This is occurring in the NCI-sponsored Selenium and Vitamin E Cancer Prevention Trial (SELECT), a randomized, double-blind, placebo-controlled, population-based trial investigating selenium and vitamin E in the prevention of prostate cancer (Klein et al. 2001). An important feature of SELECT is the collection and preservation of blood samples that will permit the evaluation of a wide variety of biomarkers associated with hormone-related genes that are prominent in prostate carcinogenesis, such as the androgen receptor, *CYP17A1*, *SRD5A2*, and *HSD3B2* (Hoque et al. 2001). NCI also is working with the Women's Health Initiative (WHI) to assess biomarkers. The WHI is a set of clinical trials and an observational study in approximately 160,000 healthy, postmenopausal women to test the effects of postmenopausal hormone therapy, diet modification, and calcium and vitamin D supplements on heart disease, fractures, and breast and colorectal cancer. The biomarker study includes a genome-wide single nucleotide polymorphism scan for markers

associated with breast cancer, cardiovascular disease, and stroke and should be completed by 2010 (Prentice and Qi 2006).

Aside from providing a fingerprint of a disease state, biomarkers also are needed to define "normal" so that change, for example, from a premalignant to malignant state, can be monitored. Identifying changes at the earliest possible stages in the carcinogenic process will be of great benefit, as will biomarkers that can distinguish between changes indicative of a general response versus changes indicative of a response that is specific to the cancer cell. Furthermore, researchers will need to understand the significance of changes in biomarkers in the context of carcinogenesis. Identifying and validating biomarkers that reflect changes occurring during the transition from a premalignant to a cancerous cell will be of great use in cancer prevention research, an area with the potential to impact favorably public cancer prevention measures and ultimately survival.

1.7 Systems Biology

Basic and clinical research during the last half of the twentieth century has yielded data reflecting the vast complexity of components and interactions of biological systems at multiple levels: molecular, cellular, and organ. To provide meaningful order and develop a systematic approach that addresses this complexity, a relatively new biological study field—systems biology—has emerged that focuses on complex interactions in biological systems. Systems biology may be viewed as a field of study or as a set of protocols, or approaches, which are used to conduct research. As a field of study, systems biology involves investigations into how interactions give rise to the function and behavior of a biological system. Examples include interactions of enzymes and metabolites in a metabolic pathway (Snoep and Westerhoff 2005). As a set of protocols for conducting research, systems biology is not limited to the integration of the complex observations making up a biological system. Rather, this incarnation of systems biology imbues it with a more global role: it includes the underlying theory driving the research, computational modeling to develop testable hypotheses about a biological system, and experimental validation; these protocols then use the knowledge gained to create a quantitative description of cells or cell processes to refine the computational model or theory (Kholodenko et al. 2005). This is the focus of systems biology most relevant to cancer prevention research, which is using techniques and methods in proteomics, metabolomics, transcriptomics, and high-throughput technology to collect quantitative data for the development and validation of disease and risk models.

Recently, whole genome approaches have led to the identification of genetic loci that are relevant to complex diseases in a way that the candidate gene approach could not do. In a somewhat analogous fashion, systems biology goes beyond the single molecule or pathway to understand (1) the higher level properties and dynamics of complex biosystems, including both the interactions among their parts and with other systems, (2) how these systems are established and perturbed, and (3) what happens to them when they are perturbed. Because cancer can arise from perturbation of a number of different yet interconnected pathways, a systems biology approach may prove useful in developing better prevention and treatment strategies (Hornberg et al. 2006). In the area of molecularly targeted therapies, for example, the promising results obtained with early efforts in this direction are often thwarted by resistance to the targeted interventions or by an extremely limited spectrum of candidate tumors. As data on the molecular interactions underlying cancer accumulate, analysis of multiple inputs or parameters at the same time will be critical to designing better targeted and individually tailored interventions that interfere simultaneously with collateral, or alternative, molecular paths to the cancer in question (Liu et al. 2006). In a well-established example, tamoxifen is a drug that targets a

specific molecule, the ER, and its use has yielded substantially increased survival among women with ER+ breast cancer. Yet tamoxifen fails to benefit some individuals, and some ER+ breast cancers never respond to this ER targeting agent. Analysis of multiple pathways that affect cell proliferation shows that ER+ breast cancers with high growth factor receptor expression [particularly epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2)] are more likely to be resistant to endocrine therapy. High levels of the protein known as ER coactivator amplified in breast cancer (AIB1) also appear to reduce the effectiveness of tamoxifen (Massarweh and Schiff 2006). Thus, a multipronged approach that targets multiple, growth-promoting molecules and pathways, namely those alternative pathways that bypass the originally intended target (in this example, the ER), may lessen the possibility of resistance and provide a more permanent cure.

1.8 Future Directions for Attaining Optimal Impact in Cancer Prevention

Cancer prevention research has expanded tremendously over the past three decades. Information on lifestyle and medical interventions has become more evidence-based as methodologies have become more rigorous. Yet the knowledge gained has not been optimally used in translation of findings to patients and the public, leaving major challenges to the implementation of effective cancer prevention strategies and interventions. For a few interventions for which acceptance and uptake in the clinical and community settings have occurred—tamoxifen use to prevent contralateral, or secondary primary, breast cancers and smoking cessation among men leading to decreases in lung cancer mortality—impressive progress has been made. These examples of success point to the potentially enormous public health benefits that would be experienced if other documented prevention interventions could be translated into widespread use.

Development of a multidisciplinary approach to cancer prevention investigations, using both lifestyle and medical strategies, is critical. The incorporation of "-omic" technologies and methodologies into such multidisciplinary investigations lends increasing credence to the possibility that an individual's risk level can be assessed, thus allowing individualized recommendations for cancer prevention. This may include recommendations for nutritional interventions, the ideal level and type of physical activity, and tailored chemoprevention regimens based on genetic and/or metabolic profiles. Such an approach has been suggested by nutrition researchers, as comprehensive DNA and metabolic profiles have come closer to reality (Arab 2004). An individual's DNA or metabolic profile would serve several important purposes for disease prevention and control. First, it would allow the design of clinical intervention studies to focus recruitment of those individuals with identified genomic or epigenomic profiles who are likely to benefit from a given intervention. A second potential benefit would be that by honing in on such very high-risk individuals in clinical prevention trials, the number of participants in such trials could be decreased, since the anticipated event rate (breast cancer occurrence) would be expected to increase. Hand in hand with increased event rate is the expectation that the time it takes to observe the effects of the intervention at a statistically significant level would shorten. Another anticipated benefit from establishing baseline metabolic profiles of trial participants is that these molecular entities will serve not only as markers of increased risk but may also function as biomarkers whose measurement and modulation in response to interventions has potential to serve as surrogates for clinical efficacy. Together, these modifications in trial design should lead to the need for fewer

human and economic resources in conducting cancer prevention trials.

Important challenges exist also in the training of a new generation of multidisciplinary investigators who are comfortable working with emerging technologies, but have expertise in cancer, to make optimal use of knowledge gained for cancer prevention. Training is supported through many types of NIH grants, but increased support of scientists early in their careers is necessary. Inclusion of training in the many medical, biological, physical, engineering, and other sciences important to cancer research, such as nutrigenomic, genomic, and metabolic research, should be made available. In addition, the training of individuals from multiple disciplines (e.g., basic, biomedical, clinical, engineering, and information sciences) who are interested in pursuing research on nanotechnology tools and/or applications for the prevention of cancer needs emphasis.

A challenge for making optimal use of current resources is how to collect, manage, and use the overwhelming amount of data generated by "-omic" technologies. For example, multidimensional protein identification technology (MudPIT) enables the analysis of as many as 60,000 proteins at a time (Chen et al. 2006). For useful analysis of these large proteomic datasets in cancer prevention, the proteome must be better defined related to its role in cancer promotion and progression, a better understanding of the differential expression of proteins in different cell compartments must be developed, and the proteome must be measured with a high degree of quantitative accuracy. Targeted arrays that address specific questions or biological pathways of interest also may be useful for resolving the difficulties attendant in handling large datasets. Ultimately, the integration of genomics, proteomics, and metabolomics will be essential for predictive interpretations in prevention research.

Even with enhanced information gathering provided by emerging technologies in concert with basic and experimental research, optimization of the potential of cancer prevention will not occur without a concerted effort to translate this information from the bench to the bedside and to the community.

Prevention is a major overall strategy for reducing the burden of cancer on society. We are not making optimal use of the potential of cancer prevention, but progress is encouraging, as shown by the continued decline in incidence of certain cancers. A comprehensive approach making use of new technologies, informatics, and nanotechnology, along with enhanced multidisciplinary training, will provide a sound base of experimental researchers to develop investigative strategies to address both lifestyle and medical strategies to prevent cancer.

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