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Commentary

COMMENTARY

Cancer Prevention: Obstacles, Challenges and the Road Ahead

Frank L. Meyskens Jr, Hasan Mukhtar, Cheryl L. Rock, Jack Cuzick, Thomas W. Kensler, Chung S. Yang, Scott D. Ramsey, Scott M. Lippman, David S. Alberts

Affiliations of authors: Biological Chemistry, Public Health, and Epidemiology, Chao Family Comprehensive Cancer Center, School of Medicine - University of California, Irvine, Irvine, CA (FLMJr); Arizona Board of Regents Professor of Medicine, Pharmacology, Public Health, Nutritional Sciences & BIO5, University of Arizona Cancer Center, Skin Cancer Institute, Tucson, AZ (DSA); Wolfson Institute of Preventive Medicine and Head, Centre for Cancer Prevention; Centre for Cancer Prevention, Queen Mary University of London, Mile End Road, London, UK (JC); Department of Pharmacology and Chemical Biology, University of Pittsburgh, Pittsburgh, PA (TWK); Moores Cancer Center (SML) and Department of Family Medicine and Public Health, Cancer Prevention and Control Program (CLR), UC San Diego, San Diego, CA (SML); Dermatology Research Laboratories, University of Wisconsin; Madison, WI (HM); Hutchinson Institute for Cancer Outcomes Research, Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA (SDR); Center for Cancer Prevention Research, Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers University, Piscataway, NJ (CSY).

Correspondence to: Frank L. Meyskens Jr, MD, FACP, Biological Chemistry, Public Health, and Epidemiology, Chao Family Comprehensive Cancer Center, School of Medicine, University of California, Irvine, 251 Irvine Hall, Irvine, CA 92697 (e-mail: flmeyske@uci.edu).

Abstract

Approaches to reduce the global burden of cancer include two major strategies: screening and early detection and active preventive intervention. The latter is the topic of this Commentary and spans a broad range of activities. The genetic heterogeneity and complexity of advanced cancers strongly support the rationale for early interruption of the carcinogenic process and an enhanced focus on prevention as a priority strategy to reduce the burden of cancer; however, the focus of cancer prevention management should be on individuals at high risk and on primary localized disease in which screening and detection should also play a vital role. The timing and dose of (chemo-)preventive intervention also affects response. The intervention may be ineffective if the target population is very high risk or already presenting with preneoplastic lesions with cellular changes that cannot be reversed. The field needs to move beyond general concepts of carcinogenesis to targeted organ site prevention approaches in patients at high risk, as is currently being done for breast and colorectal cancers. Establishing the benefit of new cancer preventive interventions will take years and possibly decades, depending on the outcome being evaluated. We also propose that comparative effectiveness research designs and the value of information obtained from large-scale prevention studies are necessary in order for preventive interventions to become a routine part of cancer management.

Framing the Major Issues

The specific term "chemoprevention" has been in active usage since introduction of this approach into the conscious scientific lexicon nearly four decades ago. Sporn (1) wrote that, "Progression of preneoplastic lesions can be stabilized, arrested, or reversed" (an approach evolved in the context of his work with vitamin A and the retinoids). He and many others have broadened the definition of "chemoprevention" to "the use of natural or synthetic agents to block, retard, or reverse the carcinogenic process." And now, in the past year, an almost accusatory editorial/commentary, "Chemoprevention is a failure" (2), and a rebuttal, "Chemoprevention is not a failure" (3), have appeared in the journal *Carcinogenesis* and galvanized us to offer this Commentary as an assessment of the status of cancer chemoprevention research and as a benchmark for the road ahead for the broader field of cancer-preventive intervention.

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The topic of cancer prevention research spans a range of approaches; primary, secondary, and tertiary prevention broadly capture the activities. We define these stages as follows:

- Primary Prevention: Avoidance of exposure to carcinogens, lifestyles that decrease risk (eg, never smoke), or vaccinations.
- Secondary Prevention: Slowing, blocking, or reversing progression of carcinogenesis to invasive cancer (eg, consider the importance of molecular endpoint biomarkers and their validation).
- Tertiary Prevention: Removal or suppression of precancerous lesions (eg, adenomatous polyps).

However, we first need to examine a major issue, a perceptual conundrum: the term "chemoprevention" itself and the impact it has had on the perception by the lay, scientific, and medical communities and its influence on responses to and/or judging the value of its outcomes.

On the one hand, many feel that the term chemoprevention, implying chemotherapy, has impacted negatively the uptake of even successful chemoprevention. On the other hand, the side effects from chemopreventive agents are real and perceived quite differently by the patient. The best and widely known cases are the definite "proof of principle" studies of tamoxifen for breast cancer prevention (4–6), a topic which has been extensively discussed vis à vis the failure of this highly effective intervention to be adopted in practice (7). A second major issue has been lumping together over such diverse approaches as dietary manipulation, natural products, and repurposed "benign drugs" into the chemoprevention bucket. Clearly, any intelligent analysis of these different modalities mandates that the implementation of these approaches have a well-thought-out rationale and needs to take into account both negative and positive data as well.

Whether modern genomics can increase individual risk/benefit accuracy substantially in the prevention setting remains challenging, except perhaps in a minority of cases (8) or very recently via improved refinement of genomic profiling (9). A recent high-profile analysis of stem cells and their role in cancer has also led to a highly controversial and widely discussed conclusion that the development of cancer is a random process ("stochastic") and by inference that the preventive approach is futile (10). There are, however, many dissenters to this viewpoint, pointing out correctly that at an individual-level risk can be affected in numerous positive and negative ways, both by intrinsic genetic, epigenetic, or environmental influences (11,12). The controversy continues! Actual assessment of risk benefit at the population vs individual-person level is a challenging exercise, a topic that will be discussed later in this Commentary.

A series of questions and answers will be explored from several viewpoints in this Commentary, and with some trepidation our overall answers are provided in the Summary/Road Ahead section and major recommendations offered for moving these approaches into actual practice (Table 1).

- Why has the record of population-based epidemiology to predict success of chemoprevention in humans been so heterogeneous and often not validated in clinical trials?
- What are the over-arching issues that affect the assessment of risk for cancer, and how so far has "genomics" affected that perception/evaluation?
- How have lifestyle, dietary, and pharmacologic interventions been assessed, and what approaches might improve the success and implementation rates?

Table 1. Moving the field of cancer prevention research toward meaningful practice guidelines

Recommendations
1. The development of preventive intervention strategies using chemoprevention compounds for those individuals with substantial risk secondary to inherent genetic risk and/or environmental exposures should be done cautiously, whether it involves restoring a measured deficiency to normal levels, the use of natural products (or their derivatives), or repurposed pharmaceutical compounds. The risk/benefit evaluation should be guided by the risk/benefit scales relevant to the intended recipients.
2. New chemopreventive compounds need to be developed that are assessed early in the process for relevant pharmacodynamics properties in phase O/I type settings before moving to clinical phase II or III trials.
3. Aspects of lifestyle including energy intake, food choice, physical activity, and other environmental exposures contribute to cancer risk in the primary prevention setting. The contribution of individual lifestyle-related factors should be assessed as an aggregate, with the development of validated risk scores and an overall lifestyle intervention approach developed for individuals.
4. Prevention research should lead to discoveries that improve both quality and quantity of life, and both are legitimate outcomes for assessing effectiveness. The results from screening and early detection studies also affect application of these recommendations (recent reviews include 104–106). Screening appointments should expand their goals to also provide information about cancer risk and advise on how to reduce the risk. Screening and prevention need to become more integrated into direct clinical care, as the screening appointment is a teachable moment for providing cancer prevention advice. Likewise, the limitations of surrogate biomarkers need to be acknowledged (107).

- Why has the strong and positive preclinical science been so unsuccessful in predicting favorable clinical outcomes of chemoprevention in humans at risk for cancer?
- How have pharmacologic candidate interventions been identified, developed, and evaluated in the clinical setting: What have been the major confounders? How can we do better?
- What major principles of the biology of carcinogenesis have been unrecognized, newly recognized, and/or ignored in developing the science of chemoprevention? How can we improve our approach?
- How should the special case of cancer survivorship be approached vis à vis chemoprevention?
- How might Comparative Effectiveness Research (CER) contribute to assessing whether to move ahead with a particular intervention? Retrospectively? At each stage of clinical development?

The major elements that have led to this landscape of questions will be presented at various locations in this Commentary, some of which have been reviewed by others from different points of view (2,13–14).

What Population-Based Epidemiology Can Tell Us About Individual Risk and What It Cannot

Population vs Individuals

A major dilemma in statistics is that the fundamental power of the methodology is based on aggregating individuals into groups to eliminate random noise, and a continuing issue is how

these groups can then be disaggregated to make predictions about individuals. Increasingly sophisticated methods have been developed, ranging from simple subgroup stratifications through linear or log-linear regression, more complicated parametric models with interactions, and complex nonparametric models such as spline regression, nearest neighbor, or kernel-smoothing techniques. The fundamental trade-off between different models is a balance between bias because of an inaccurate model specification and random variation because of small effect sample sizes for individual predictions. This is exemplified by the large number of false subgroup interactions claimed with treatment (15–17) and now many examples of similar problems with risk markers (18,19). With large sample sizes, more detailed models can be fit that account for all of the predictable variation based on known covariates, but even then a component of variation because of random error, which is unpredictable, will remain. At a philosophical level, there is the basic issue of whether the future is predictable, as illustrated by the difference between quantum vs classical mechanics (20). At a more practical level, the desire for a complete understanding of the full complexity of the human-cancer interaction is beyond reach and is not realistic. However, in many cases much of the variation in risk between individuals can be accounted for, and here a key distinction is to separate host (genetic) factors from environmental (lifestyle) factors. While the intense activity in genetic risk factor discovery has identified a few highly penetrant major alleles and a host of lower penetrance single-nucleotide polymorphisms (SNPs) for specific cancers (21–23) that in aggregate can help to refine risk estimates, the genes responsible for much of the polygenic risk currently remain unidentified (24). Even for monozygotic twins, cancer occurrence is not concordant, reflecting the importance of environmental exposures. Genetics play a larger role in rare cancer syndromes such as familial adenomatous polyposis coli (FAP), where carriers are almost certain to develop cancer if untreated (25) and risks in excess of 50% have been established for a range of other rare genetic mutations (26). For environmental/lifestyle exposures, population-attributable risk in excess of 50% is rare, and the only major example is smoking and lung cancer (27). For other cancers, including breast, prostate, and colon, models that combine genetic and environmental factors are needed to better quantify risk. One example is breast cancer, where a model containing major genes, low penetrance SNPs, and lifestyle has been explored by Brentnall et al. (28). Using their calculations, the difference in risk between the upper vs lower quintile is about 4.6-fold and cancer incidence would be reduced by 61% if all women's risk was reduced to that for the lowest quintile, although this is not possible because of the immutable genetic factors involved. A similar less mature effort that is trying to dissect the role of genetic variants in affecting the activity of aspirin and NSAIDS and colorectal cancer risk has recently been reported (29).

Patients at High Risk or Low Risk: Which Group to Pursue?

Risk models can be assessed on two complimentary scales. The most important is predictive power, which can be measured on the spread of risk produced in the population, either in terms of the proportion exceeding a specified risk threshold or by more general but less easily comprehended measures such as the concordance index or area under a receiver operating characteristic curve (AUC). A second measure is one of calibration, which determines the extent to which the predicted risk corresponds to the actual risk observed in a given population. A risk assessment tool can be highly predictive but still be poorly calibrated if, for example, its estimated risk distribution and population segregation is larger than that actually observed in a given population. This is easier to address by a recalibration than by predictive power, which generally requires the addition of new measurements.

Focusing preventive activities on high-risk individuals is very important for many agents for two main reasons. Firstly, risk-benefit ratios are generally lower than for disease treatment, so that treatment-related side effects are of greater importance. Highly effective agents tend to have a greater side effect profile than less active ones, and most individuals are risk averse, so fear of side effects is a major factor affecting their acceptance and compliance. Focusing efforts on high-risk individuals not only improves the benefit-risk ratio but also is an important factor in achieving good adherence to treatment, which tends to be required for a long period of time. The second reason is that some preventive agents are expensive and for these treatments a focus on those likely to benefit most is clearly needed. For some agents such as aspirin, where benefits are seen for a range of cancers and other diseases and the costs are negligible, identifying individuals at high risk is less important and risk assessment is most needed to identify those at greatest risk of side effects. Risk assessment can also identify those at low risk of specific disease, where preventive activities, including routine screening, are much less important and efforts are best focused on other aspects of health. For other modalities such as increased physical activity, there are few side effects and benefits are sufficiently widespread that risk assessment is of less value, as almost all individuals stand to benefit from the intervention or lifestyle change, although the benefits are still higher in those at higher risk, such as the obese.

In summary, although precise prediction of who will get which cancer will never be possible, risk assessment is a useful tool and can help to focus preventive activities for a particular cancer to those at highest risk. A longer-term goal is to predict which preventive agents will be effective for risk reduction of cancers caused by specific mutations and exposures. Developing more accurate models for risk using both genetic (high-penetrance and lower-penetrance alleles) and environmental/lifestyle factors is an important part of a cancer preventive strategy and needs to be more actively pursued.

The Complexity and Inter-Relatedness of Lifestyle and Dietary Interventions

Results from numerous observational studies conducted over the past several decades suggest that lifestyle factors such as weight control, diet, and level of physical activity are important modifiable determinants of cancer risk and progression (30). Diet and physical activity and the outcomes of those behaviors, overweight and obesity, appear to contribute to 30% to 40% of cancer cases (30). The science of sedentary behavior is an emerging focus of cancer prevention research (31) because sedentary behavior, independent of physical activity level, is associated with increased risk of colorectal, endometrial, and ovarian cancer (30–35), as well as weight gain in colorectal cancer survivors (36). Compared with diet interventions, there is a dearth of clinical trials of the effect of increased physical activity on cancer risk and progression. However, a randomized controlled trial that is testing the effect of a structured physical activity intervention on disease-free survival in colon cancer survivors is currently underway (37).

When examining or testing exposures or assessing determinants of risk, developing evidence related to dietary factors is particularly challenging because food and eating patterns are complex and multifaceted by nature (38,39). A bioactive food component or drug may have multiple molecular interactions potentially useful in one pathway but not in another. Combinatorial approaches are likely to be required, as has been well and long recognized in cancer therapeutics. For example, a diet high in vegetables and fruit provides numerous potentially beneficial constituents, such as folate, polyphenols, carotenoids, and fiber (40,41); so a focus on a specific nutrient or bioactive food component may not be effective. Even a focus on specific foods can be misleading because foods are consumed as part of an overall dietary pattern that has other characteristics, having differential amounts of less healthful constituents as well as a complex and variable mixture of potentially healthful dietary factors (39). Further, lifestyle behaviors such as diet quality, physical activity, weight management, and smoking status are typically clustered (42), so teasing out the effect of a single element or behavior is difficult if not impossible. Variability in the human intestinal microbiota and resulting microbial metabolites further complicates the interpretation of associations with dietary factors and effects of interventions (43). As the composition of the diet influences gut microbiota, which in turn affects the bioavailability and metabolism of bioactive food components and likely other agents (44,45), the recent recognition of the importance of the microbiome in health and disease adds another dimension of complexity between identified exposures in observational studies and response of individuals to interventions. Also, there are fundamental analytic problems in assessing the response to one component in the diet in the presence of others. The conundrum evolving from this realization, largely ignored, makes predicting outcomes in response to a single dietary compound unreliable (Supplementary Materials, Section 1, available online) (46).

If cancer outcome is the primary focus, clinical trials require a very large sample size and a substantial investment of resources. Results from intervention trials targeting high-risk individuals or those with preneoplastic lesions may not be generalizable to the broader population, and depending on the proposed molecular mechanism the timing of the intervention may not be appropriate (47). For example, knowledge of the adenoma-carcinoma sequence in colorectal cancer is fairly well known compared with lesion relevance in other cancers (48): More evidence from molecular pathological epidemiology may enable better targeting of diet and other lifestyle interventions (49,50).

Shorter-term intervention studies, which are less expensive and involve smaller samples, are a strategy to identify the effects of modification of these lifestyle factors on markers of cellular activities instead of cancer outcomes. However, observed short-term effects on biomarkers or proposed mechanistic factors do not necessarily translate into effects on cancer or other clinical outcomes (51,52). Also, in any clinical trial of a lifestyle intervention, the trial is actually testing the intervention itself in addition to testing the effect of a specific diet or level of physical activity. Achieving adherence to the prescribed behavior or dietary change is a challenging goal. Testing the effect of foods or dietary constituents in feeding studies or supervised exercise activities on cancer biomarkers produces only very short-term changes that may not be sustained and, thus, may not necessarily affect cancer outcomes.

Treatment duration in diet intervention trials is limited, usually not exceeding an average of five years. Given the long latency of most cancers, this brief timeframe is not a true test of the diet-cancer connection. Also, the intervention may be too late in the cancer continuum; this issue is particularly important in the design and interpretation of diet intervention trials because nutritional effects on physiological factors are known to be particularly critical during developmental periods.

In summary, we propose that one strategy to better test the relationship between dietary factors and other lifestyle factors and cancer is to target a group that is likely to benefit from behavioral modification. Realistic, convenient, and achievable goals are necessary, and strategies to support maintenance of behavior change are crucial. Finally, a focus on foods and dietary patterns, rather than a reductionist approach, may produce findings that are transferable to public policy and recommendations. A detailed review of dietary and natural products studies with references is provided (Supplementary Materials, Section 1, available online).

Overarching Issues That Affect Individual Outcomes: Age, Sex, Ethnicities, Cultures, and Comorbidities

While evidence from basic science research supports the potential for biologically active food components and pharmacological agents to affect cancer risk and progression, evidence from both observational epidemiologic studies and randomized clinical trials has been inconsistent, in some instances more than others (2). In both of these types of studies, the target population presents with variable personal characteristics, including genetic factors that may be powerful determinants of the likelihood of observing an association or response.

Age and sex affect the background metabolism and physiology, which can affect response, and genetic factors clearly influence response to potentially chemopreventive dietary constituents and drugs (53). Numerous genetic factors have been shown to influence the absorption and metabolism of food components as well, which in turn will affect response and outcomes (54–56). For example, the ability of fish oil to decrease TNF-α production or respond favorably to omega-3 fatty acid is influenced by a polymorphism in the TNF-α gene (56,57). Polymorphisms in genes for cyclooxygenase-2 and IL-6 have been found to be associated with differential concentrations of serum inflammation markers, although they were not observed to modify the response to a Mediterranean diet supplemented with olive oil or nuts in a high-risk population (58). Differential responses and outcomes across racial/ethnic groups may be attributable in part to the differing prevalence of various polymorphisms. For example, racial differences within the androgen receptor pathway may be one cause of differences in the biology of prostate cancer among racial groups (59,60). Sociocultural influences are also among the personal characteristics that may influence outcome, especially in behavioral interventions in which adherence is more complicated than simply taking a supplement (61).

The presence of comorbidities also affects outcomes in cancer prevention trials. For example, type 2 diabetes mellitus was statistically significantly associated with reduced overall survival regardless of treatment group assignment in a large diet intervention trial testing the effect of dietary modification on breast cancer recurrence (62). A major overarching issue in the interpretation of results of preventive intervention trials is that they are conducted over a time period of a few years, which is brief relative to the long latency of most cancers (63).

In summary, the development and impact of age, sex, ethnicity, culture, and comorbidities on preventive intervention needs to be recognized in the design and interpretation of all trials. The impact of comorbidities on interventional effectiveness and outcomes needs to be routinely assessed, particularly in older individuals, as comorbidities accumulate with age and affect both the intervention and health and mortality outcome.

Relevance and Limitations of Preclinical In Vitro and Animal Studies

For a long time, it has been known that chemical agents can readily protect experimental animals against cancer development (64). In the laboratory, in vitro models have been used to study detailed mechanisms, but the results have not been robust enough to be used as translational evidence for moving directly to clinical trials. Therefore, animal models, mainly rodent, have been a cornerstone for preclinical testing of chemopreventive agents (65,66). It is quite frustrating that translating these laboratory data to human cancer has not yet yielded the desired results (2,3,67).

Preclinical evaluation of chemopreventive agents is limited by the fact that many of the animal models available to date do have limited physiological relevance to human disease (64–66). The development of mammalian models to study tumorigenesis should require physiological relevance to human disease if they are to be useful for deciding "go/no go" into translational prevention trials. It is difficult to recapitulate the complexities of human tumors in preclinical animal models. Models developed to date only mimic a few individual characteristics of aggressive tumors, although patient-derived xenografts hold promise as useful tools to identify therapeutic targets (68,69). However, extension of this approach to cancer preventive intervention remains to be tested. Also, in conducting mouse studies with single or a combination of agents, we generally optimize protocols for maximum tumor yield in the control group and look for effects of the agents; also, we gather preclinical data in mouse models of well-delineated genetic background while keeping them under strictly controlled laboratory conditions with access to only a well-defined dietary regimen. This is not possible in conducting human intervention trials. Humans enrolled in clinical trials usually have diverse genetic backgrounds and have engaged in wide-ranging dietary habits and other life style factors such as smoking, alcohol consumption, and food preparation methods that may affect biologically active constituents, and thus exposures.

In conclusion, animal models for chemoprevention testing should: 1) produce cancerous lesions of comparable pathology to that of humans; 2) the genetic abnormalities of these lesions should be similar to those found in humans; 3) the model should be capable of producing a consistent tumor burden; 4) the carcinogen or genetic defect used to produce cancer should bear relevance to that encountered by humans; and 5) the usefulness of in vitro and animal models as approaches to moving to translational trials needs to be reassessed, a difficult task that has been recently undertaken by the National Cancer Institute (65). The predictive values and accuracy of the animal model for human efficacy should be highly consistent. This is not an easy goal to achieve. In addition, studies of possible preventive agents in multiple animal models are needed.

Dose, Duration, Timing and Combinations

Lesson Learned From Phase III Chemoprevention Trials

The best-studied active agents in cancer chemoprevention, tamoxifen, aspirin, and NSAIDs, illustrate some of the key drug development issues. Data from selective estrogen receptor modulators (SERMs) in breast cancer prevention illustrate the complexity of these drug issues (4,70). Early landmark trials indicated tamoxifen efficacy in reducing the risk by as much as 50% of ER-positive breast cancer (4), an effect that endures long after treatment cessation (71). Breast cancer trials of tamoxifen in the adjuvant setting suggested a dose- and duration-dependent risk of side effects. Consequently, work is ongoing in the preventive setting to optimize the tamoxifen regimen through dose reduction, combinations with other agents, intermittent dosing, and the development and study of newer analogues and related agents with a potentially higher therapeutic (or should it be prophylactic?) index. Treatment with the second-generation SERM raloxifene in postmenopausal women was found to produce similar preventive effects as tamoxifen but without an increase in the risk of uterine cancer. These studies resulted in the US Food and Drug Administration approval of raloxifene as an alternative treatment to tamoxifen for breast cancer risk reduction in high-risk women. However, treatment with raloxifene is still associated with increased risk of hot flushes and thromboembolic events. In addition, its preventive effects wear off after three years, to retain only about 75% of the effectiveness of tamoxifen for the prevention of breast cancers (72). Given that there appears to be a trade-off between side effects and effectiveness over the long term, the selection of tamoxifen vs raloxifene as a preventive therapy is dependent upon the patient. As it is less likely to cause uterine cancer than is tamoxifen, raloxifene may be best for postmenopausal women at high risk of breast cancer with an intact uterus. However, in postmenopausal women without a uterus tamoxifen may be the drug of choice because it shows enhanced effectiveness over the long term.

Accumulating long-term evidence supports an effect of aspirin in reducing overall cancer incidence and mortality in the general population (73,74). Data from randomized controlled trials support the use of aspirin to protect against colorectal cancer and are in agreement with much of the observational data. Although the dose and duration of aspirin differ among the trials, it appears that higher doses of aspirin over longer time periods are needed to obtain a protective effect. Additional trials are needed to determine the optimum dosing regimen and answer remaining questions regarding which molecular subtypes of colorectal cancer might be prevented. In addition to aspirin, NSAIDs have been and continue to be a focus of chemopreventive agent development for colorectal cancer. Sulindac has demonstrated mixed results in four small trials involving FAP patients (75). A primary prevention trial testing the ability of sulindac to prevent adenoma development in phenotypically unaffected FAP carriers failed to demonstrate an effect (76). Sulindac results in FAP patients with adenomas have been largely positive (77), demonstrating regression of adenomas. Combined sulindac-DFMO treatment proved successful, resulting in a remarkable 70% reduction in recurrent sporadic adenomas vs placebo, with no statistically significant differences in adverse effects (78).

Greater Emphasis on Intensive Early-Phase Clinical Trials Needed

The genetic heterogeneity and complexity of advanced cancers strongly supports the rationale for early timing in intervention in the carcinogenic process and an enhanced focus on prevention as a priority strategy to reduce the burden of cancer (68). As dosing frequencies, routes, attendant risks, and acceptable toxicities are narrower in the preventive setting than they are in

the therapeutic setting, early-phase clinical studies must clearly define the optimal dose, duration, and potential toxicities before larger, more expensive trials are undertaken.

More attention must be placed on the quantitation of how much of the administered preventive intervention agent actually reaches the target lesion in humans. We try to do this with chemotherapy drugs, and we must do this much more carefully for preventive agents. Several key criteria have been established for potential preventive agents to fulfill, most notably that the drug should be detectable in the organ of interest and optimally modulate a biomarker that is predictive of clinical effect. The latter is a lofty and hard-to-achieve goal, but advances in functional imaging may allow this approach to be realized in the near future (79). There is also often a need to adapt agents to be safer and more acceptable through a variety of strategies. The combination of two or more agents for prevention requires in-depth preclinical studies and phase 1 trials to evaluate adverse drug interactions, scheduling of the agents in the combination, and availability after oral administration (eg, doses of one of the agents reduces the systemic availability of the other).

Moving Toward Precision Cancer Chemoprevention

Targeting specific biochemical pathways has been a mainstay of cancer therapy, whether the endpoint be an enzyme (eg, methotrexate of 5-FU) or, in more modern parlance, a specific protein such as a tyrosine kinase and $BRAf_{mut}$ inhibitors (80,81) or other molecular targets. Attempts to emulate this approach vis à vis "chemoprevention" have been highly successful in defining putative mechanisms in vitro (81) and in standard and transgenic mouse models (65). However, translation of this approach to population health or for clinical benefit has been considerably more challenging for multiple reasons, as discussed in prior sections. In addition, adverse or off-target effects may obviate acceptance of an otherwise successful intervention. In the end, what is determinant for the adoption of chemoprevention will be the relative risk-benefit tolerance level in the management of "premalignancies" in early vs late carcinogenesis and the prevention setting. The issue of target and mechanism is particularly challenging when it comes to the assessment of natural products because these compounds frequently do not have a single molecular target (82). The experience with many phytochemicals suggests that they interact with multiple biochemical steps (83–85). The green tea polyphenol (epigallocatechin-3-gallate, EGCG) may be the best-studied example of this phenomenon (86–88). The widely spread plant flavonoid luteolin also holds promise but has yet to enter clinical trials (89–91).

In summary, we propose: If adverse events (if any) occur, the clinical risk benefit should be the driver for human clinical trials, not the requirement for a singular molecular target. We would further argue that the assessment of the value of chemoprevention should not depend on mechanism per se but on relative risk benefit as assessed clinically and informed by the broader view offered by comparative effectiveness analysis (below).

The Carcinogenic Continuum and Preventive Intervention Response

Advances in our molecular understanding of the biology of the process of carcinogenesis at the genomic and at all levels of postgenomic processing and its relationship to tumor formation have resulted in a series of challenges for the development of preventive interventions. Another generic issue that affects the interpretation of trial outcomes is that the biology and biochemistry of cancer is known to be heterogeneous: a clinical cancer can arise from a number of aberrant pathways through various genetic mutations (92). The timing of the chemopreventive intervention may also affect response; it may be too late in the cancer continuum if the target population is very high risk or already presenting with late preneoplastic lesions that possess genetic or cellular changes that cannot be reversed (93). Although these various principles derived from an ever-increasing molecular understanding of the process of carcinogenesis are well recognized and applied in treatment paradigms, they have in general not been an integral part of preventive intervention trials. These and other concepts are further discussed in the Supplementary Materials (Section 2), most notably the concept of carcinogenesis as a noncontinuum process ("Interpretation of the Nature of Carcinogenesis and Its Effect on Preventive Interventions").

Prevention and Cancer Survivorship

With the number of cancer survivors increasing at a rapid pace in recent years, the potential importance of prevention intervention has increased although it is in its infancy. The now-prominent health issues in cancer survivorship have been known for some time (94–96), but adoption of useful practices have been slow in coming (97,98). A summary of the complex issues related to Prevention and Cancer Survivorship are provided in the Supplementary Materials, Section 3 (Ancillary Issues, available online).

Comparative Effectiveness Research (CER) and Value of Information

Also, as much of cancer preventive research involves modification of behaviors that increase risk, comparative effectiveness applications are particularly relevant. Because a cornerstone of CER is engaging multiple stakeholders, these studies must be more than simply comparing an intervention aimed at a behavior vs "usual" habits. Studies must be designed with feasibility of implementation in mind, taking into account the perspectives of the affected individuals, those who would support and fund the intervention, and those who would be affected downstream (eg, health insurers, families). Fortunately, a recent article described a roadmap for CER studies in prevention (99). A more detailed discussion of these issues is provided in the Supplementary Materials, Section 3 (Ancillary Issues, available online).

Summary of Answers to Major Initial Questions and the Road Ahead

We offer these answers to the questions posed in the introduction to this Commentary: The record of population-based epidemiology in predicting the success of chemoprevention in humans has been heterogeneous and often not validated in clinical trials because populations are not individual people.

- Lifestyle, aging, and comorbidities are the major over-arching events that affect the assessment of risk for cancer. "Genomics" has introduced some precision, but the tools are inherently inexact.
- For primary prevention, a moderate increase in physical exercise, weight loss, decreased caloric consumption, and an improved vegetable-based diet should be integrated into practice and lead to a "healthy lifestyle."
- In preclinical studies, conditions are well controlled and usually set to maximize the cancer-preventive effect, which often cannot be duplicated in human studies. In vitro studies can only provide mechanistic guidance. The physiology of mice is not that of men or women.

- New, more effective (enhanced benefit and diminished risk) chemoprevention agents need to be developed before chemoprevention will become more widely adopted. A major reassessment of how drugs are developed for chemoprevention needs to be undertaken with a major emphasis on Phase 0 and I pharmacodynamics studies before moving forward to correlative phase II studies.
- The process of carcinogenesis is not a biological continuum but a series of steps, and an agent that works on one step may not work on another and may produce unexpected adverse effects.
- Chemoprevention is not ready for routine adoption in cancer survivors. Emphasis currently should be on primary prevention and the management of long-term side effects.
- The principles of CER should be integrated into practice decision-making at all levels of clinical prevention practice.

In the spirit of enhancing the likelihood that cancer prevention research will be translated into evidence-based practice prevention guidelines, we offer five major recommendations (Table 1). The broad field of cancer prevention engages a wide range of experts, not dissimilar from that of our cardiovascular disease colleagues although the field of cancer chemoprevention is 10 to 20 years behind the synthetic prevention and treatment paradigm that has evolved for cardiovascular disease (100–102). Nevertheless, following cancer prevention guidelines reduces the risk of cardiovascular disease (103)!

At the current time, we also need to ask: Are we prepared to achieve the level of engagement in health that has been obtained by peer countries? Are we prepared to redistribute resources to prevention (and less in treatment) research and its application?

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