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Can a Marker Be a Surrogate for Development of Cancer, and Would We Know It if It Exists?

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Abstract Carcinogenesis proceeds through a very long preclinical period. Our collective hope is that multiple opportunities exist for chemoprevention to arrest or reverse progression towards malignancy. In the hope of faster progress with fewer subjects and lower total cost, much effort is being expended on the search for reliable biomarkers to predict the likelihood of developing cancer and/or to signal the effectiveness of chemopreventive therapy. Considerable attention is paid to identifying those markers that can act as surrogate markers for cancer development, since favorable modulation of the surrogate endpoint biomarker (SEBM) may demonstrate effectiveness of a putative preventive treatment. However, the complexity of the biology challenges our ability to measure the effectiveness of attempts to arrest or reverse carcinogenesis, other than through costly and time-consuming prospective trials with disease state as the endpoint. Despite much work, to date no prehistologic biological or molecular intermediate marker has been validated for sporadic cancers. Several factors accounting for the difficulties encountered in SEBM development are reviewed. Discussion is focused on the common thread of the complexity of the underlying biological changes in carcinogenesis limiting the effectiveness of any single biomarker. Additionally, the incidence of sporadic cancers is also low, further limiting the positive predictive value of any putative prognostic marker. Recent successes in development of chemopreventive agents show the concept is valid and worth pursuing, but the current strategies to develop biochemical and genetic markers to identify surrogate biomarkers is flawed, and need to be reassessed in light of the difficulties faced over the last 20 years.

1 Introduction

The old saying, "An ounce of prevention is worth a pound of cure," would seem especially true for cancers, and indeed that belief has motivated a great deal of research and other activities in the "fight" against cancers. Clearly there has been some success in cancer prevention, resulting from efforts in smoking cessation, weight reduction, cervical screening, and other lifestyle modifications. However, success from chemoprevention has been much more elusive. The path from identifying a likely chemoprevention agent through demonstrating that the drug is safe and reduces cancer risk in a large population is full of pitfalls. Basically, our understanding of the biology of cancers is still insufficient to make effective chemoprevention mechanisms obvious. We must proceed empirically at each step, at notable cost in time, effort, and money. Many believe appropriate use of surrogate endpoints could improve the efficiency of our work.

At the present level of understanding, cancer is not one disease but many disease entities. The histology and biology of tumors differ widely among organ sites. For tumors of the same histology in different organs, the genetic events leading to cancer are often different, and there seems to be variability in etiologic mechanism even within a cancer type. Thus, it is said there are multiple pathways to malignancy, and so a chemoprevention agent that successfully guards against one chain of biochemical events may be defeated by the redundancy of carcinogenic mechanisms. With improved understanding of all the relevant carcinogenic mechanisms, we might some day find an exploitable early common event to develop a chemoprevention agent analogous to the broad-spectrum antibiotic, but that is far beyond us at present.

To date, over one thousand candidate chemopreventive agents have been identified, making selection of the most promising compounds for detailed investigation a difficult task [26]. Selecting promising compounds for further study should be as rational as possible, since a great deal of effort is involved in confirming the usefulness of a putative chemopreventive agent. Trials must be long-term because the disease takes many years to develop, and long-term commitments from study participants with corresponding maintenance of staffing and infrastructure are necessary. Evaluation of putative preventive agents in trials where malignancy is the endpoint is expensive and cumbersome.

A valid surrogate holds the potential to place fewer subjects at risk and to answer important questions in a more economical fashion, while moving the field forward faster [40]. Attempting to improve efficiency, methods to identify markers of disease that can act as surrogate endpoints have been aggressively pursued, both to screen out ineffective chemopreventive agents and to make clinical evaluation of promising agents faster—using smaller numbers of subjects—and therefore cheaper.

Surrogate endpoints have seen some success in cardiology and other areas of medicine. However, in oncology, the same biologic complexity and pathway redundancy that challenges putative prevention agents challenges the identification of surrogate endpoint biomarkers. Unfortunately, despite much work, to date there are no validated prehistologic biological or molecular surrogate endpoint biomarkers for sporadic cancers. As long-time proponents of chemoprevention and the development of biomarkers, we now question if attempts to identify and validate surrogate endpoints to measure effectiveness of chemopreventive agents is a viable strategy, given the biological realities of carcinogenesis and the difficulties encountered.

2 Biomarkers and Surrogate Endpoints

By definition, a biological marker (biomarker) is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention" [10]. A small subset of biomarkers demonstrates a strong correlation with the desired clinical endpoint and can serve as a substitute for the clinical endpoint. These surrogate endpoints are expected to be reasonably likely to predict clinical benefit or harm (or lack thereof) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence [10].

What is required for a biomarker to be considered a surrogate endpoint? The United States Food and Drug Administration (FDA) has an expedited drug approval pathway for serious and life-threatening conditions based on use of surrogate endpoints, specified in the Food and Drug Modernization Act of 1997 [8]. According to FDA regulations, the standard is not rigidly defined. A "reasonably likely" standard was adopted in the regulations to accept study results utilizing a surrogate endpoint for granting expedited approval of therapeutic agents. Recognizing that this standard represents a compromise that could affect safety, additional requirements for further post hoc study following approval to describe clinical benefit and safety were included in the regulations.

The (American) FDA criteria for accepting a surrogate endpoint result are less rigorous than the criteria espoused by experts to validate a surrogate endpoint [10, 37]. For a biomarker to be a valid surrogate endpoint, it must meet two fundamental criteria [17, 37]. First, it must closely correlate with the target clinical endpoint. One expert has suggested 2.5%–10% false-positive and false-negative results as minimally acceptable levels for candidate surrogate endpoints [17]. This is a necessary, but not sufficient condition. For example, CD4 count and HIV viral load correlate with subsequent mortality from AIDS [18]. However, this does not mean that changes in these biomarkers will reliably measure effectiveness of a new drug to treat HIV in-

fection. For example, these markers do not adequately reflect toxic effects or interactions between agents in a multi-drug regimen [29].

The second requirement for validation is that the surrogate endpoint must fully capture the net effect of the treatment on clinical outcome [37]. Even a strong statistical association of biomarker levels with clinical outcome is no guarantee that a drug that modulates the biomarker will affect the target endpoint. A statistical association between the biomarker and clinical outcome does not indicate a unique or sufficient causative relationship. Clearly, the likelihood a surrogate will be effective is enhanced by choosing biomarkers integrally tied to the causal pathway(s) leading to the target endpoint.

To be useful, a surrogate endpoint's predictive abilities must hold across different treatment populations and with different therapeutic agents. A biomarker that faithfully predicts the clinical endpoint in one population must also demonstrate the same relationship in different treatment populations. In addition, the relationship of the biomarker to the clinical endpoint must hold up across treatments. If treatment with drug A demonstrates a favorable effect on the surrogate endpoint, which is verified by favorable modulation of the target clinical endpoint, then changes in the surrogate endpoint by treatment with drug B must also correlate with changes in the clinical endpoint in a corresponding fashion.

A valid surrogate endpoint captures the net effect of the drug on all the pathways affecting the clinical endpoint, accounts for toxicity, and shows little variability across populations. These requirements are extremely rigid, and in practice, no surrogate endpoint to date perfectly correlates with the true endpoint. In complex systems with multiple pathways and redundancy, the existence of a biomarker that faithfully reflects changes along all the important pathways becomes highly improbable.

Finding a single surrogate marker that serves well across all populations and treatments seems unlikely. One fallback position for the strategy is to concede this point and determine the "performance envelope" of candidate markers. Multiple studies across treatments and populations will be required to characterize the biomarker and demonstrate its characteristics as a surrogate endpoint. This modified strategy requires no less work and offers less in terms of overall efficiency of the discovery process. The ultimate judgment of surrogate endpoint utility will vary by disease process and intervention, and the standards required for judgment will differ correspondingly. For chemoprevention of cancer, the burden of proof is very high to be able to determine that a compound has clinical effectiveness and minimal to no toxicity, as any successful compound will be taken for many years by asymptomatic individuals.

3
Experience with Surrogate Endpoints in Drug Development

To provide a framework to better understand difficulties encountered using surrogate endpoints in cancer prevention trials, review of experience with surrogate endpoints in drug development for other disorders is instructive. In an earlier commentary [12] we indicated that surrogate endpoint development has been relatively successful for cardiovascular disease and AIDS. However, close analysis demonstrates that successful employment of surrogate endpoints has not been easily accomplished, has not been uniformly successful, and has been associated with some spectacular and instructive failures along the way.

The reliance on surrogate endpoints can lead to patient harm [17]. A sampling of studies where surrogate endpoints in clinical trials of a variety of drugs demonstrated favorable effects, but failed to demonstrate clinical benefit, or showed increased mortality is displayed in Table 1. A striking example of the potential risk of relying on surrogate endpoints is the experience with several antiarrhythmic agent trials to decrease premature ventricular contractions (PVC) when administered after myocardial infarction. Although the drugs did decrease PVCs, there was a significant increase in mortality with drug use. Increased mortality was also found in trials of promising agents shown to demonstrate increased exercise tolerance and cardiac output when used to treat congestive heart failure [35, 36].

The experience with drugs to treat hypertension has been more favorable. Two large prospective trials have demonstrated decreased total mortality with pharmacological management of hypertension [2, 4]. Control of blood pressure is now accepted as a surrogate endpoint for antihypertensive agents based on extensive experience. More recently, drugs including angiotensin-converting enzyme inhibitors and calcium channel blockers have been approved based on the surrogate endpoint of efficacy at decreasing blood pressure and perceived improved side-effect profile. There is concern by some that these drugs have not been compared directly with previously approved drugs, indicating a lack of faith in the surrogate-endpoint strategy, and long-term mortality studies have not been completed. However, as pointed out by Temple [43], these drugs have undergone extensive study in related diseases, and their side-effect profiles are well understood; so it seems a reasonable bet they will safely predict lack of toxicity for hypertension.

A number of cholesterol-lowering drugs have been developed based on the observed correlation of favorable levels of cholesterol, HDL, and LDL levels with lowered mortality [25]. Clofibrate and niacin were early drugs used to decrease cholesterol. The drugs effectively lowered cholesterol levels, but overall mortality was increased [1]. Early meta-analyses of randomized controlled trials of cholesterol-lowering interventions demonstrated decreased cholesterol and cardiac mortality, but overall the interventions were

Table 1. Surrogate endpoint experience in cardiology and other disciplines

Clinical Problem	Drug	Surrogate	Clinical endpoint	Outcome	Reference
Cardiovascular					
Arrhythmias	Encainide Flecainide	Arrhythmias	Survival	Increased mortality	[15]
	Moricizine	Arrhythmias	Survival	Increased mortality	[5]
Atrial fibrillation	Quinidine	Atrial fibrillation	Survival	Increased mortality	[14]
	Lidocaine	Atrial fibrillation	Survival	Increased mortality	[23]
Congestive heart failure	Milrinone	Cardiac output Ejection fraction	Survival	Increased morality	[35]
	Flosequinan	Cardiac output Ejection fraction	Survival	Increased mortality	[36]
Abnormal lipid/lipoproteins	Clofibrate/Niacin	Cholesterol	Survival	No decreased mortality	[1]
	Simvastatin	Cholesterol	Survival	Decreased mortality	[7]
Hypertension	High-dose diuretics	Blood pressure	Survival	No improvement in survival	[41]
	Calcium channel blockers	Blood pressure	MI/survival	Increased mortality in meta analysis	[21]
Osteoporosis	Sodium fluoride (post menopausal)	Bone density	Fractures	Increased fractures	[38]
HIV and AIDS	Antiretroviral agents	CD4	AIDS events survival	Failure to predict clinical outcome	[39]
	Antiretroviral agents	HIV mRNA	AIDS events survival	Failure to reflect treatment on clinical outcome	[9]
Chronic granulomatous disease	Interferon	Superoxide production, bacterial killing	Serious infections	Endpoint improved, surrogate did not	[3]
Critical care	Growth hormone	Nitrogen balance	Survival	Increased mortality	[42]
Hormone replacement therapy	Estrogen/progestin	Cholesterol/LDL/HDL	CHD, death, nonfatal MI	No decreased coronary heart disease	[31]
	Estrogen/progestin	Coronary artery diameter	CHD, death, nonfatal MI	No effect on coronary stenosis	[24]

CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction.

associated with increased mortality from noncardiac causes, and a slight increase in overall mortality [19]. More recently, 3-hydroxy-3-methylgluaryl coenzyme A (HMG Co-A) reductase inhibitors have demonstrated improvements in mortality in a large, well conducted phase III trial [11]. The trial also discovered the threshold for benefit from these agents was much lower than previously thought, and persons characterized as being at low risk for cardiovascular disease could benefit from the lipid-lowering drug [11]. This information would not have been known without the large prospective trial measuring the true clinical endpoint.

Promising candidate surrogate endpoints have failed to predict clinical outcome in several other diseases. Counts of CD4 cells or viral DNA levels correlate with disease prognosis, but changes in these markers with drug treatment have not been as useful as hoped, especially in the settings of multi-drug regimens with significant toxicities and development of drug resistance [17, 18]. Sodium fluoride treatment was believed to be helpful for prevention of pathological fractures in persons with osteoporosis. Bone mineral density was proposed as a logical surrogate endpoint based on correlations of fractures and bone density [38]. Unfortunately, although bone density was increased by treatment, so were fractures, and it was learned that the bones became more brittle with treatment [38]. Most recently, hormone replacement therapy in postmenopausal women predicted to decrease cardiac risk instead failed to slow disease progression, and may have increased cardiovascular mortality [24, 31]. It was accepted almost as gospel that postmenopausal hormone therapy had a favorable effect on cardiovascular risk [22]. Two large studies failed to show benefit [24, 31], and one study suggests combination estrogen plus progestin increases the risk of coronary heart disease [31].

Discarding a useful agent is also a risk of using imperfect surrogate endpoints. The experience with interferon-gamma treatment for chronic granulomatous disease is instructive. Interferon-gamma was evaluated in a clinical trial in patients with chronic granulomatous disease [3]. The surrogate endpoints measured were bacterial killing and superoxide production. Drug treatment failed to modulate the surrogate endpoint, but interferon-gamma effectively decreased the number of serious infections in treated subjects [3]. This is an important reminder that reliance on an ineffective or inappropriate surrogate endpoint can result in discarding an effective agent.

Analyzing the experiences with developing surrogate endpoints in other fields reveals at least two lessons. First, many of the early studies evaluating surrogate endpoints failed because of inadequate knowledge of the drug's effects on the biological pathways and incomplete knowledge of the biochemical pathways (e.g., clofibrate and niacin for hyperlipidemia). Second, only after effective agents that demonstrably improved the clinical outcome were identified were surrogate endpoints accepted for drug approvals [e.g., angiotensin-converting enzyme (ACE) inhibitors for hypertension]. Identification

of promising biomarkers and promising drugs to treat a disease relies in large part on understanding the underlying disease pathophysiology. Determining the effectiveness of the biomarker as a surrogate endpoint in turn depends on having clinically effective drugs. The chemoprevention field is many years away from this point. Developmentally, the current status resembles cardiovascular disease research of the 1970s. Thus, perhaps the chemoprevention community should "bite the bullet" and concentrate on the identification of effective agents, delaying attempts at validation of surrogate markers until theoretical frameworks are in place to support such efforts. Such markers would serve to improve the efficiency of identifying second- or later-generation agents.

4 Challenges to Using Surrogate Endpoints in Chemoprevention Drug Development

There are two broad risks associated with use of surrogate endpoints. The first risk is the surrogate fails to adequately predict the true endpoint. The second risk is failure to identify competing or adverse effects on related or unrelated pathways. Competing drug effects on alternate pathways not captured by the surrogate can cancel out favorable drug effects, resulting in favorable modulation of the surrogate, but less-than-predicted or no favorable effect on the clinical endpoint. Unrecognized toxic effects can also exert an adverse impact on the clinical endpoint.

A very basic mathematical fact makes the use of surrogates to evaluate effectiveness of cancer chemopreventive agents very difficult outside of special populations. The ability of a given imperfect surrogate to predict disease is intimately tied to the prevalence of predisposing conditions in the population studied. As the prevalence of predisposing conditions decreases, the positive predictive value of an imperfect marker declines. Because sporadic cancers in the general population are rare, the discriminating ability of imperfect surrogates will be of limited clinical use, at best.

There are several reasons why surrogate endpoints fail to faithfully predict clinical endpoints. The surrogate endpoint may measure effects on a distinct parallel pathophysiological pathway, it may measure effects on only one of multiple important pathways, there may be unknown mechanisms that block clinical effect, or there may be toxic effects that have an adverse effect on the true endpoint. There may also be population differences that limit the applicability of the marker to populations not involved in "validating" it. Sporadic cancers are generated in a multi-step, multi-year, multi-pathway process, and selection of a single or group of markers along single or multiple pathways will not capture a high enough proportion of the risk of transformation to cancer to be useful [12, 13, 20]. Further limitations oc-

cur because we have not completely worked out all of the relevant carcinogenic pathways to cancer and identified all the critical checkpoints [12].

In a previous commentary we discussed how the mathematics of combinations illuminates the size of the problem inherent in monitoring changes on multiple carcinogenic pathways [12]. When multiple pathways contributing to cancer development can be disrupted, and when disruption of several (but not all) of these pathways is necessary to induce cancer, the number of possible combinations of distinct biomarker patterns that lead to cancer becomes very large, and the task of identifying and verifying the utility of each biomarker pattern is daunting. The number of subjects required to check and characterize each of the possible combinations of biomarkers could exceed the number of subjects in a phase II trial [12, 16].

Since single biomarkers are likely to be defeated by the redundancy of biochemical pathways to cancer, perhaps sets of biomarkers adequate to the task may be identified. A logical extension leads to the analyses of profiles of gene or protein expression. It is very seductive to hope that the ability to simultaneously measure genetic changes in thousands of genes using gene chip arrays will transform our ability to detect precancerous changes and monitor the effectiveness of chemopreventive treatments. An incredible amount of information is generated that must be analyzed to identify patterns of changes that predict cancer. Because of the multiple pathways and multiple points where disruption can occur, a very large number of samples will be required to identify all the patterns that predict the development of sporadic cancers, even of a particular type. In addition, the changes detected need to be early enough along the chain of carcinogenic events to be amenable to arrest or reversal by candidate chemopreventive agents. The same requirements for determining utility of the biomarker(s) derived from gene array studies apply, and the effect of alterations on the biomarker must be verified by determining the effect on cancer incidence. This does not mean the importance of gene chip technology in chemoprevention should in any way be discounted. To the contrary, the technology provides a powerful tool to better understand the pathophysiology leading to cancer, and the knowledge gained will stimulate new avenues of investigation that may lead to new candidate preventive and therapeutic agents.

An important issue confronting researchers using surrogate endpoints is the applicability of the surrogate endpoint. To be effective, the surrogate must be applicable not only to all members of the group tested but also to subsequent populations receiving the same treatment. This can only be determined by multiple studies on diverse groups of subjects. A second major problem is applicability across interventions. Because of the heterogeneity of the mechanisms of carcinogenesis across tumor types, it is doubtful that a nonhistological marker will either reliably measure effectiveness of different classes of chemopreventive agents against the same tumor, or pre-

dictably measure effectiveness of a single drug across multiple tumor histologies and locations.

The second broad risk of relying on surrogates is failure to identify counteractive effects on the clinical endpoint that are not reflected by the surrogate, or effects that produce unacceptable toxicity. Several examples in cardiovascular drug development have already been discussed. The experience with beta-carotene as a chemopreventive agent exemplifies the problems that can be faced even with seemingly innocuous compounds. It was not until phase III trials were conducted that a procarcinogenic effect of beta-carotene in persons who smoked while taking the drug was discovered [6, 33]. This paradoxical effect in the subgroup at highest risk for developing lung cancer was a sobering experience for the field, and likely would not have been detected in smaller trials using surrogate endpoints as the basis for approval.

5 Intraepithelial Neoplasia as a Surrogate Endpoint

Comparison of lessons learned from cardiovascular and other pharmacological drug development trials using surrogates with recent publications by leaders in chemoprevention indicates there is incomplete recognition or acceptance of the limitations of surrogate endpoints [28, 34]. O'Shaugnessy et al. [34] acknowledge limitations of surrogate endpoints, but assume that eradication of intraepithelial neoplasia (IEN) in itself will be of clinical benefit and predict decreased mortality for a number of cancer sites. The assumption that elimination of the IEN by chemopreventive agents will decrease cancer incidence seems logical, but needs to be proved. Given the number of failures of surrogate endpoints in other disciplines, IEN eradication by a chemoprevention drug cannot be assumed to predict decreased cancer incidence or mortality. The argument that a tangible clinical benefit is attained simply by eradication of the IEN (independent of cancer prevention) has weaknesses. For many sites, the presence of the IEN is not the problem, as most lesions at most sites are asymptomatic. It is the prevention of what the lesion may become (cancer) that is of clinical benefit, representing a change and not a static event.

Eradication of visible and histological evidence of the disease does not mean elimination of the genetic changes that can produce cancer, but an ineffective or partially effective chemopreventive agent could change a visible lesion that would develop into cancer to an invisible lesion that still develops into cancer. Unless genetic changes in the tissues can be conclusively reversed or managed, reliance on clinical regression of IEN as a surrogate is risky and needs to be eventually verified in definitive phase III trials with cancer incidence as the clinical endpoint.

In the oral cavity, it is estimated that over half of cancers do not have a preexisting clinically recognizable lesion before development of cancer. Clinical regression of the lesion does not mean the risk of transformation also disappears. There is a risk of converting a visible lesion to an invisible lesion that will still develop cancer. A similar problem is seen with nonsteroidal anti-inflammatory agents and colon cancer. Celecoxib was approved for cancer prevention for familial adenomatous polyposis (FAP) based on decreased numbers of polyps. Studies of sulindac for FAP found that polyps were more difficult to screen because they were flattened in appearance [32, 45]. The recently reported prostate cancer prevention trial (PCPT) [44] reported delay or prevention of low-grade prostate cancer and an increased proportion of high-grade prostate cancer. The question remains; are the subjects receiving benefit?

That clinical and histological regression of IEN can serve as a valid surrogate for cancer development has not been proved. There may be clinical benefit to treatment of IEN, but there are potential risks in using this approach, and these risks are too great to warrant approval of a chemopreventive agent based solely on its effect on IEN. For these reasons, we need to first focus on the true endpoints, cancer incidence and mortality, and then determine if changes in IEN do in fact reliably predict decreased cancer incidence and mortality.

Kelloff [27, 28] provides a theoretical construct using clinical and genetic changes in IEN as a surrogate endpoint. He acknowledges that clinical regression does not guarantee clinical response, and thus advocates use of molecular testing to demonstrate arrest or reversal of carcinogenesis at the molecular level. Here again, the theory is very logical. Unfortunately, we have not yet worked out all the relevant pathways to cancer, so we do not know all the genes and proteins that need to be monitored. Confirmation will require old fashioned, time-consuming, phase III clinical trials to answer the key question of whether cancer has been suppressed or eliminated sufficiently to warrant a lifetime consumption of a drug.

In the invited commentary accompanying O'Shaughnessy's article, Lippman et al. [30] suggest that while complete eradication of premalignant clones may not be possible, delaying the onset of cancer would convey real clinical benefit. This is a sensible position to take given the current state of knowledge about oncogenesis, but it does not remove the obligation to demonstrate decreased incidence of cancer or cancer mortality. If a treatment is effective, and it does in fact delay onset of cancer, this will be borne out in time-to-event analysis where the event is frank malignancy. Again, one cannot assume that delay in development of IEN or an intermediate endpoint will translate to actual clinical benefit.

6 Conclusion

Surrogate endpoints are not a "Holy Grail" that can guide us to effective chemoprevention agents. Biomarkers, however, can be useful in the early stages of chemoprevention drug development if used appropriately. The quest to demonstrate a marker that is a useful signal of both agent activity and risk of malignancy may consume more resources than it is intended to save. Future efforts should focus on identification of biomarkers that are mechanistically related to carcinogenic pathways affected by the drug, and are modulated by the drug. Thoughtful investigation of biomarkers in chemopreventive drug development can provide valuable knowledge about important carcinogenic pathways and the interactions of therapeutic agents with these pathways. If and only if an early common carcinogenic event (or limited number of early events) is identified, and only if that event can be exploited will efforts at developing surrogate endpoint biomarkers have a chance of being successfully employed. In the meantime, we should instead be using biomarkers as "shovels" to dig for the answers about the mechanisms of carcinogenesis and to select promising chemopreventive agents for further study.

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References

1. [No authors listed] (1975) Clofibrate and niacin in coronary heart disease. JAMA 231:360–381
2. [No authors listed] (1979) Five-year findings of the hypertension detection and follow-up program. I. Reduction in mortality of persons with high blood pressure, including mild hypertension. Hypertension Detection and Follow-up Program Cooperative Group. JAMA 242:2562–2567
3. [No authors listed] (1991) A controlled trial of interferon gamma to prevent infection in chronic granulomatous disease. The International Chronic Granulomatous Disease Cooperative Study Group. N Engl J Med 324:509–516
4. [No authors listed] (1991) Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA 265:3255–3264
5. [No authors listed] (1992) Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. The Cardiac Arrhythmia Suppression Trial II Investigators. N Engl J Med 327:227–233
6. [No authors listed] (1994) The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. N Engl J Med 330:1029–1035
7. [No authors listed] (1994) Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 344:1383–1389

8. [No authors listed] (1997) Food and Drug Modernization Act. Title 21Code of Federal Regulations Part 314 Subpart H Sections 314.500–314.520
9. [No authors listed] (2000) Human immunodeficiency virus type 1 RNA level and CD4 count as prognostic markers and surrogate end points: a meta-analysis. HIV Surrogate Marker Collaborative Group. AIDS Res Hum Retroviruses 16:1123–1133
10. [No authors listed] (2001) Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 69:89–95
11. [No authors listed] (2002) MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 360:7–22
12. Armstrong WB, Taylor TH, Meyskens FL Jr (2003) Point: Surrogate end point biomarkers are likely to be limited in their usefulness in the development of cancer chemoprevention agents against sporadic cancers. Cancer Epidemiol Biomarkers Prev 12:589–592
13. Califano J, van der Riet P, Westra W, et al (1996) Genetic progression model for head and neck cancer: Implications for field cancerization. Cancer Res 56:2488–2492
14. Coplen SE, Antman EM, Berlin JA, et al (1990) Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials. Circulation 82:1106–1116
15. Echt DS, Liebson PR, Mitchell LB, et al (1991) Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. N Engl J Med 324:781–788
16. Edwards AL (1967) Statistical methods. Holt Rinehart and Winston, New York
17. Fleming TR, DeMets DL (1996) Surrogate end points in clinical trials: are we being misled? Ann Intern Med 125:605–613
18. Gilbert PB, DeGruttola V, Hammer SM, et al (2001) Virologic and regimen termination surrogate end points in AIDS clinical trials. JAMA 285:777–784
19. Gordon DJ (1994) Cholesterol lowering and total mortality. In: Rifkind BM (ed) Contemporary issues in cholesterol lowering: clinical and population aspects. Marcel Dekker, New York
20. Hahn WC, Counter CM, Lundberg AS, et al (1999) Creation of human tumour cells with defined genetic elements [see comments]. Nature 400:464–468
21. Held PH, Yusuf S, Furberg CD (1989) Calcium channel blockers in acute myocardial infarction and unstable angina: an overview. BMJ 299:1187–1192
22. Herrington DM, Howard TD (2003) From presumed benefit to potential harm—hormone therapy and heart disease. N Engl J Med 349:519–521
23. Hine LK, Laird N, Hewitt P, et al (1989) Meta-analytic evidence against prophylactic use of lidocaine in acute myocardial infarction. Arch Intern Med 149:2694–2698
24. Hodis HN, Mack WJ, Azen SP, et al (2003) Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. N Engl J Med 349:535–545
25. Kannel WB, Castelli WP, Gordon T (1979) Cholesterol in the prediction of atherosclerotic disease. New perspectives based on the Framingham study. Ann Intern Med 90:85–91
26. Kelloff GJ, Malone WF, Boone CW, et al (1990) Progress in applied chemoprevention research. Semin Oncol 17:438–455
27. Kelloff GJ, O'Shaughnessy JA, Gordon GB, et al (2003) Counterpoint: because some surrogate end point biomarkers measure the neoplastic process they will have high utility in the development of cancer chemopreventive agents against sporadic cancers. Cancer Epidemiol Biomarkers Prev 12:593–596

28. Kelloff GJ, Sigman CC, Johnson KM, et al (2000) Perspectives on surrogate end points in the development of drugs that reduce the risk of cancer. Cancer Epidemiol Biomarkers Prev 9:127–137
29. Lederman HM, Williams PL, Wu JW, et al (2003) Incomplete immune reconstitution after initiation of highly active antiretroviral therapy in human immunodeficiency virus-infected patients with severe CD4+ cell depletion. J Infect Dis 188:1794–1803
30. Lippman SM, Hong WK (2002) Cancer prevention by delay. Commentary re: JA O'Shaughnessy et al. Treatment and prevention of intraepithelial neoplasia: an important target for accelerated new agent development. Clin Cancer Res 8:314–346, 2002. Clin Cancer Res 8:305–346
31. Manson JE, Hsia J, Johnson KC, et al (2003) Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 349:523–534
32. Matsuhashi N, Nakajima A, Shinohara K, et al (1998) Rectal cancer after sulindac therapy for a sporadic adenomatous colonic polyp. Am J Gastroenterol 93:2261–2266
33. Omenn GS, Goodman GE, Thornquist MD, et al (1996) Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial [see comments]. J Natl Cancer Inst 88:1550–1559
34. O'Shaughnessy JA, Kelloff GJ, Gordon GB, et al (2002) Treatment and prevention of intraepithelial neoplasia: an important target for accelerated new agent development. Clin Cancer Res 8:314–346
35. Packer M, Carver JR, Rodeheffer RJ, et al (1991) Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. N Engl J Med 325:1468–1475
36. Packer M, Rouleau J, Swedberg K, et al (1993) Effect of flosequinan on survival in chronic heart failure: preliminary results of the PROFILE study (abstract). Circulation 88(Suppl 1):I
37. Prentice RL (1989) Surrogate endpoints in clinical trials: definition and operational criteria. Stat Med 8:431–440
38. Riggs BL, Hodgson SF, O'Fallon WM, et al (1990) Effect of fluoride treatment on the fracture rate in postmenopausal women with osteoporosis. N Engl J Med 322:802–829
39. Sande MA, Carpenter CC, Cobbs CG, et al (1993) Antiretroviral therapy for adult HIV-infected patients. Recommendations from a state-of-the-art conference. National Institute of Allergy and Infectious Diseases State-of-the-Art Panel on Anti-Retroviral Therapy for Adult HIV-Infected Patients. JAMA 270:2583–2589
40. Schatzkin AGail M (2002) The promise and peril of surrogate end points in cancer research. Nat Rev Cancer 2:19–27
41. Siscovick DS, Raghunathan TE, Psaty BM, et al (1994) Diuretic therapy for hypertension and the risk of primary cardiac arrest. N Engl J Med 330:1852–1857
42. Takala J, Ruokonen E, Webster NR, et al (1999) Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med 341:785–792
43. Temple R (1999) Are surrogate markers adequate to assess cardiovascular disease drugs? JAMA 282:790–795
44. Thompson IM, Goodman PJ, Tangen CM, et al (2003) The influence of finasteride on the development of prostate cancer. N Engl J Med 349:215–224
45. Tonelli F, Valanzano R, Messerini L, et al (2000) Long-term treatment with sulindac in familial adenomatous polyposis: is there an actual efficacy in prevention of rectal cancer? J Surg Oncol 74:15–20