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Increasing the Power of Surrogate Endpoint Biomarkers: The Aggregation of Predictive Factors

Harry B. Burke, MD, PhD

University of Nevada School of Medicine, Washoe Medical Center, Reno, NV 89520

Abstract A variable that predicts an outcome with sufficient accuracy is called a predictive factor. Predictive factors can be divided into three types based on the outcomes to be predicted and on the accuracy with which they can be predicted. These three types include risk factors, where the main outcome of interest is incidence and the predictive accuracy is less than 100%; diagnostic factors, where the main outcome of interest is also incidence but the predictive accuracy is almost 100%; and prognostic factors, where the main outcome of interest is death and the predictive accuracy is variable. Surrogate outcomes are predictive factors that are used for a purpose beyond the prediction of an outcome—surrogate outcomes are predictive factors that are substituted for the true outcome in order to determine the effectiveness of an intervention. Surrogate outcomes used in clinical trials are called intermediate endpoints and surrogate endpoints.

Predictive factors used as surrogate outcomes have a poor accuracy rate in predicting the true outcome; aggregating risk factors increases predictive accuracy. Artificial neural networks effectively combine predictive factors. Aggregating predictive factors increases the degree of linkage of the surrogate outcome to the true outcome. The resulting increase in predictive accuracy allows enrollment of people most likely to benefit from intervention. This increases the trial's efficiency, reducing the number of people required to assess a chemopreventive agent.

Key words: Chemoprevention, predictive factors, risk factors, surrogate endpoint biomarkers, surrogate outcomes

The risk, diagnostic, and prognostic cancer domains have their own literature and nomenclature. With the advent of molecular genetics, risk assessment, surrogate outcomes and chemoprevention, early detection, and new prognostic factors the divisions between these domains have blurred. This has led to some confusion as each domain's terminology is applied to the overlap between the domains. In this paper we propose to standardize several terms common to these three domains, and to demonstrate a method for combining predictive factors to increase prediction accuracy.

Address correspondence to Harry B. Burke, MD, PhD, University of Nevada School of Medicine, Washoe Medical Center, 77 Pringle Way, Reno, NV 89520.

PREDICTIVE FACTORS

For a predictive factor to be useful, its value must change in a predictable way when an intervention changes the outcome. An outcome is anything we are interested in predicting. In cancer, certain outcomes are important because they guide therapy. The three most common outcomes in cancer are incidence, recurrence, and death. Predictive factors can be outcome-specific; a variable may be a predictive factor for one outcome but not for another. Factors are level-of-analysis dependent; a particular factor exists only at a particular level of analysis. The terms "marker," "biomarker," "predictor," "prognosticator," and "indicator" have been used interchangeably with the term "factor," but they are not always synonymous. For example, most

predictive factors are markers of disease, but few markers of disease are predictive.

To determine whether a variable is a predictive factor, and if so, to determine its predictive accuracy, an outcome must be selected and the variable must be tested in a population. The population must be followed until a sufficient number of people in that population have achieved that outcome. If the variable predicts the outcome we are interested in with a sufficient accuracy, we call it a predictive factor. Sufficiency depends on the domain under study, and accuracy depends on the strength of the relationship between variable and outcome, the quality of data collection, and the ability of the predictive model to capture the relationship between variable and outcome. For prediction with a single factor, people with that factor are subsequently predicted to live as long as those with that factor in the original population. If the predicted outcome always occurs, we say that the predictive factor and the outcome are 100% linked, *i.e.*, that the factor has a 100% predictive accuracy.

RISK, DIAGNOSTIC, AND PROGNOSTIC FACTORS

Predictive factors can be divided into three types based on the outcomes to be predicted and the accuracy with which they can be predicted (Table I). These three types include risk factors, where the main outcome of interest is incidence and the predictive accuracy is less than 100%; diagnostic factors, where the main outcome of interest is also incidence but the predictive accuracy is almost 100%; and prognostic factors, where the main outcome of interest is death and the predictive accuracy is variable.

The term "risk" has several meanings. It can be used as a general term to denote the probability of the occurrence of an outcome, but it can also be used to denote a particular kind of predictive factor. This can be confusing, *e.g.*, the risk of disease given certain risk factors. In order to avoid this confusion, we will replace the general meaning of the term "risk" with the term "probability." Thus, we can speak of the probability of death given certain risk factors.

Risk factors are factors that either alone, or in combination with other factors, are less than 100% predictive of disease (incidence). They represent a propensity for disease at some future date. When a group of risk factors can be combined so that there is an almost 100% certainty of the disease at some future date, they become preclinical diagnostic factors (defined in the following paragraph) and are equivalent to screening for the disease. People at substantial risk require chemoprevention to prevent them from expressing the disease.

Diagnostic factors are factors that either alone, or in combination with other factors, are almost 100% predictive of disease. They can predict that disease exists at the time the factor is determined, or that it will exist at a usually unspecified time in the future. Two types of diagnoses—the existence of preclinical disease or clinical disease—can be made. In the preclinical disease state there is no evidence of invasive disease; in the clinical disease state there is evidence of invasive disease. Incidence occurs when invasive disease is detected by a diagnostic test. The preclinical disease state is almost always discovered by screening using biological and/or radiological tests, or by accident. The clinical disease state can be asymptomatic or symptomatic. Asymptomatic clinical disease is also almost always discovered by screening or accident, whereas the discovery of symptomatic disease is usually the result of a directed search. Early detection is the existence of one or more positive diagnostic factors in the preclinical or asymptomatic patient. Preclinical patients require chemoprotection, to protect them from expressing the disease.

Prognostic factors exist in patients with the disease and predict the outcome of interest. They are susceptible to change when therapy changes the future course of the disease. Prognostic factors are usually less than 100% predictive of the outcome, and are usually combined to increase their prognostic accuracy. They may be prognostic only for certain outcomes and certain times in the disease process, or they may be prognostic for all outcomes at any time in the course of the disease. For example, predicting the outcome recurrence may require different prognostic factors than predicting the outcome survival. The relationship between predictive factors, disease states, and interventions is shown in Figure 1.

Some diagnostic and prognostic factors are related; some diagnostic factors are prognostic

TABLE I. Three Types of Predictive Factors

PREDICTIVE FACTOR	ACCURACY	MAIN OUTCOME OF INTEREST
Risk	Much less than 100%	Incidence
Diagnostic	Close to 100%	Incidence
Prognostic	Variable	Death

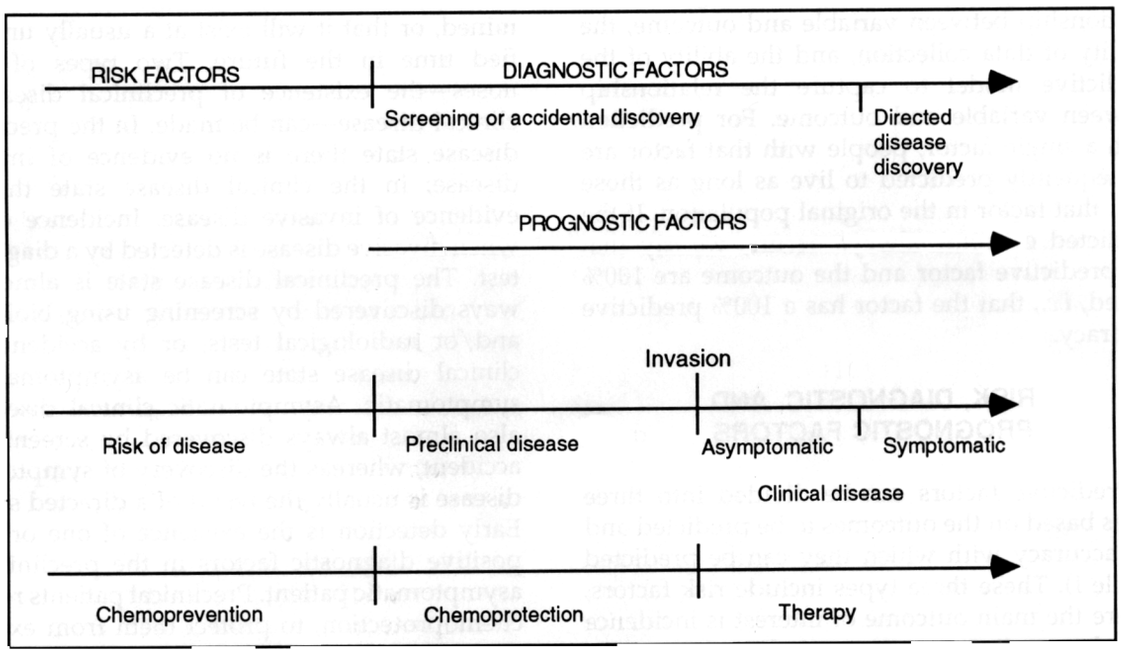

Fig. 1. Relationships between predictive factors, disease states, and interventions.

and some prognostic factors are diagnostic. Diagnostic and prognostic factors are distinguished by different purposes; diagnostic factors are used to predict the outcome existence-of-disease (incidence), and prognostic factors are used to predict outcomes related to the course of the disease. Thus, diagnostic factor analysis is similar, but not identical to, prognostic factor analysis.

Irrespective of the type of cancer, in order for an intervention to be maximally beneficial to the population at risk for the disease, to the patients with preclinical disease, and to the patients with clinical disease, three conditions must be met. First, since individual factor predictions are rarely close to 100% accurate, there must be a way to aggregate predictive factors. Second, the level at which the intervention (chemoprevention, chemoprotection, or therapy) will be instituted must be determined. Third, the intervention must be effective. Clearly the level at which the intervention will be instituted depends on accuracy of the aggregate prediction and the effectiveness of the intervention. Although at first it may seem that these three conditions do not apply to diagnosis, as we move more and more into the realm of early detection, with its greater diagnostic uncertainty, we will require

the aggregation of diagnostic factors, the setting of a level of diagnostic certainty, and the means to treat the disease we have discovered.

SURROGATE OUTCOMES

Because we do not know if an intervention is effective until the outcome of interest has occurred, and because many years can separate an intervention and the occurrence of the outcome, we would like to find something (a surrogate outcome) that changes soon after the intervention if the intervention is effective in changing the outcome. Surrogate outcomes are predictive factors that are used for a purpose beyond the prediction of an outcome; surrogate outcomes are predictive factors that are substituted for the true outcome for the purpose of determining the effectiveness of an intervention. Intermediate endpoint and surrogate endpoint refer to using surrogate endpoints in clinical trials. If there is a choice between these three terms, it is best to use the term "surrogate outcome."

Perfect Surrogate Outcomes

A perfect surrogate outcome is a factor that is 100% linked to the true outcome. We are almost always interested in a perfect surrogate outcome that precedes the true outcome. Since the perfect preceding surrogate outcome is totally linked to the true outcome, a change in the perfect preceding surrogate outcome due to an intervention will always signal a change in the true outcome. Having a perfect surrogate outcome means that we do not have to wait for the true outcome to occur to assess the effectiveness of the intervention on the true outcome. A perfect preceding surrogate outcome can be used as an index of the effectiveness of the intervention. All risk factors, diagnostic factors, and prognostic factors are potential surrogate outcomes, but few will meet the criteria for a perfect surrogate outcome.

For a factor to be a perfect surrogate outcome, two criteria must be met. First, it must be possible to discover the factor and determine its value prior to the occurrence of the true outcome. Second, there must be a 100% link between the factor and the true outcome. To determine the effect of an intervention using a surrogate outcome, one must determine the value of the surrogate outcome before and after the intervention. If the value of the surrogate outcome has changed in the desired direction, then we would expect the true outcome to change in the desired direction. A surrogate outcome may not be detected in everyone who has the disease. However, those predicted to experience the true outcome must actually do so.

Preclinical diagnostic factors can be used as a surrogate outcome for the true incidence because they accurately predict the true incidence. A clinical diagnostic factor is a lagging indicator of incidence, and therefore not a useful surrogate outcome.

Imperfect Surrogate Outcomes

Risk factors and prognostic factors are more problematic surrogate outcomes than diagnostic factors because they do not meet the second condition for a perfect surrogate outcome, namely, a tight linkage between the factor and the outcome. If the factor and the true outcome are not 100% linked, then a change in the surrogate outcome does not always reflect a change in the true outcome, and a lack of change in a surrogate outcome does not always mean that the true outcome has remained unchanged. Thus, the existence, magnitude, and direction of change in a true outcome are in doubt when the surrogate and true outcomes are not inextricably linked.

If we wish to use a factor as a surrogate outcome in spite of a weak relationship between the factor and the true outcome, there will be patients predicted to experience the true outcome who do not, and vice versa. This means that a change in the post-intervention value of a factor does not mean that we have necessarily changed the true outcome. To the degree that we can achieve close to 100% predictive accuracy, we will approach the ability to effectively use the factor as a surrogate outcome. If we allow a degree of error in the surrogate outcome's ability to predict the true outcome, we can use factors with less than 100% linkage as surrogate outcomes. In that case, we must be able to quantify the degree of linkage (the accuracy of the factor in predicting the true outcome) to determine if the prediction error is within the error tolerance. Error tolerance depends on the efficacy, side effects, and cost of the intervention, and the morbidity and mortality of the disease.

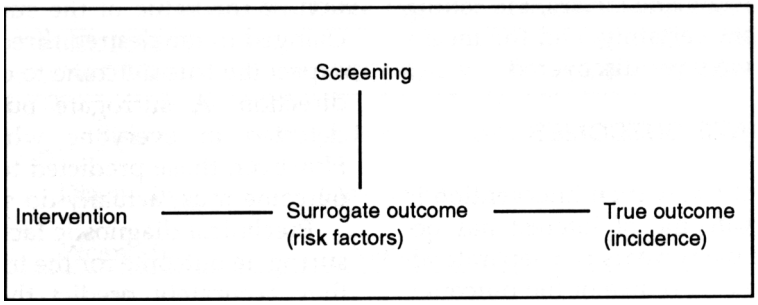

Fig. 2. Aspects of chemoprevention.

It is not clear that surrogate outcomes can reduce the time required for the initial investigation of chemopreventive agents, but it is almost certainly the case that the aggregation of risk factors can reduce the number of people that are required for the clinical trial, and that surrogate outcomes can be used in post-clinical trial chemoprevention efforts. Figure 2 shows the relationship between screening, intervention (chemoprevention), surrogate outcome (risk factor), and true outcome (incidence of disease). It is clear that the initial investigation must determine the accuracy of the screening test used to detect the surrogate outcome, the link between the surrogate outcome and the true outcome, and the efficacy of the intervention. Aggregation of risk factors into one surrogate outcome can reduce the size of the clinical trial. After the clinical trial, the surrogate outcome can allow physicians to determine whether the intervention is helping their patients, *i.e.*, they can use the surrogate outcome to monitor the efficacy of the intervention.

Cholesterol is an example of such monitoring. Cholesterol is a surrogate outcome for coronary artery disease. Patients are screened with a blood test; those with elevated cholesterol levels receive cholesterol lowering medications, and their cholesterol level is followed. Because there is a link between cholesterol levels and coronary artery disease, we believe that lowering the patient's cholesterol lowers the incidence of coronary disease. In cancer there are few risk factors strongly linked to the incidence of cancer; therefore, we must combine risk factors to increase the linkage between the surrogate outcome and the true outcome.

AGGREGATION OF PREDICTIVE FACTORS

Aggregation uses an analytic model to combine predictive factors to increase predictive accuracy. The analytic model used to combine prognostic factors for the American Joint Committee on Cancer's new prognostic system, a system that will replace the TNM staging system, is an artificial neural network.

The pTNM staging system is approximately 44% accurate in its predictions of five year survival for breast cancer. Placing the three pTNM variables in an artificial neural network increases their predictive accuracy to 52%. Combining other routinely collected variables with the pTNM variables in an artificial neural network increases predictive accuracy to 56%. Adding several of the new putative prognostic factors, *e.g.*, HER-2/*neu* and p53, to the artificial neural network further improves predictive accuracy to 70%.

Artificial neural networks are an effective method for combining predictive factors. In chemoprevention, the aggregation of predictive factors increases the degree of linkage of the surrogate outcome to the true outcome. This increased linkage increases the effectiveness of the chemopreventive agent by targeting people most likely to benefit from the intervention.

The ability to aggregate predictive factors can increase the accuracy of risk assessment, the accuracy of disease detection, and the ability to predict outcome for use in determination of therapy, patient information, quality assurance, and clinical trials.