COMMENTARY

Dangers of Using "Optimal" Cutpoints in the Evaluation of Prognostic Factors

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Much attention has been given in recent years to the study of prognostic factors in cancer, especially breast cancer. When individual prospects for survival are highly variable, it is natural to look for possible explanations. Knowledge of prognostic variables can aid in the understanding of disease and may lead to variation in treatment according to a patient's predicted probability of survival.

For many cancers, certain prognostic factors are well established, including disease stage and tumor size. Individual cancers may have additional risk factors. For example, the number of positive lymph nodes is a well-established prognostic factor for breast cancer, while other factors such as menopausal status and status of estrogen and progesterone receptors remain controversial. Despite these recognized risk factors, there remains considerable uncertainty about an individual patient's prognosis. Thus, much effort is devoted to identifying additional prognostic variables. For example, there is particular interest in distinguishing high- and low-risk groups among patients with lymph node-negative breast cancer.

Many of the new, potentially important prognostic markers are measurements derived from the analysis of DNA, such as DNA index and S-phase fraction (SPF), which is the percentage of tumor cells in the S phase obtained by cell cycle analysis. The question arises about how best to evaluate whether these measurements are really prognostic and whether they are useful, in addition, to what is already known of that disease. There are many statistical aspects of the design and analysis of studies of prognostic factors (*1,2*). Here, we concentrate on statistical analysis and evaluate one method used to investigate the prognostic importance of a continuous variable.

One common strategy for analyzing continuous variables is to convert them into categorical variables by grouping patients into two or more groups. In particular, values of a variable are frequently divided into just two groups. Categorization enables researchers to avoid strong assumptions about the relation between the marker and risk, but at the expense of throwing away information. The information loss is greatest with only two groups, but this approach is common, often by splitting at the sample median. It is well known, however, that the results of analyses can vary if different cutpoints are used. In recent years, there has been increasing interest, therefore, in evaluating the effect of taking various cutpoints and choosing the one that corresponds to the most significant relation with outcome. In other words, the cutpoint defining "low" and "high" risk is chosen that minimizes the P value relating the prognostic factor to outcome. The cutpoint so chosen is often termed "optimal," but this description is inadvisable because of the well-known problem of multiple testing, as we demonstrate below. We prefer to call it the "minimum P-value approach."

Although we know of earlier examples in other cancers (*3,4*), the most notable use of this method has been in breast cancer during the last 5 years, especially in relation to SPF. We use SPF to illustrate that this approach leads to many different optimal cutpoints, which is a first strong argument against it. That is one important reason why it is nearly impossible to compare different studies and to quantify the prognostic value of SPF. Additionally, we review some undesirable statistical properties of the minimum P-value approach to choosing a cutpoint. In particular, we show that the naive use of this approach is associated with a considerable inflation of the type I error rate. This approach may thus lead to falsely claiming a factor as prognostically relevant, although it might have no influence on prognosis at all. We propose an improvement in the sense that the P value can be corrected by the use of a relatively simple formula. This is established knowledge in the statistical literature (*5,6*), but it has been rarely applied in prognostic studies. We discuss and illustrate these and some alternative methods using data on disease-free survival from breast cancer.

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See "Notes" section following "References."

Cutpoints for SPF on Breast Cancer in the Literature

The prognostic value of the percentage of tumor cells in the DNA-synthesizing phase obtained by cell cycle analysis—in the sequel called the SPF—has been an issue of considerable controversy in recent years. We do not intend to review the literature on SPF for breast cancer patients (*7*), but the large number of different cutpoints used that are known to us demonstrates that a wide range of values from 2.6 to 15.0 have been investigated. Sometimes, these cutpoints are used only in subsets of patients, e.g., in patients with diploid and aneuploid tumors (*8*), and sometimes three SPF categories are defined using two cutpoints (*9*). For several of the cutpoints listed in Table 1, it would be possible to give additional references, and other cutpoints have been published. It is obvious that not all of the cutpoints can be optimal and that intensive searching in a new study may yield a new "optimal" cutpoint. Because the range of the cutpoints used is very wide, it has to be questioned whether there is a truly optimal cutpoint and even whether SPF has any prognostic value for disease-free and overall survival times of breast cancer patients.

In the literature, the basis for the choice of a particular cutpoint is sometimes not given (*10*), while sometimes the authors use the median SPF (*11*). Although only some of them explicitly mention that they have used the minimum *P*-value approach (*9,12*), we assume that some authors use this approach to categorize the SPF values into two groups without mentioning this in the section on statistical methods.

The cutpoint of 6.7% from Clark et al. (*12*) demonstrates that this approach may lead to an unusual categorization that may not be applicable in other laboratories (*13*). Additionally, it is to be expected that the cutpoint will change when the data are updated or when a different patient group is analyzed. In 1 year, two papers (*14,15*) were published by one research group about patients from Guy's Hospital, London. In one paper, the median SPF value of 7.1% was used to investigate the prognostic value for 140 stage I or II breast cancer patients, whereas in the other, the SPF value of 10% was used as "providing the best discrimination" for the group of 169 patients with node-negative breast cancer. Because there is probably a substantial overlap between the study populations, it may have happened that a patient was considered as a high-SPF patient in the first population associated with a poor prognosis, whereas she was categorized in the low-SPF category associated with a good prognosis in the second study.

The problems of the comparison of different cutpoints by the minimum *P*-value approach are implicitly mentioned in the paper by Joensuu et al. (*16*). An SPF value of 14% was the optimal cutpoint, and the categorization based on this value was used in their analyses. Nevertheless, Joensuu et al. write, "the SPF percentage 7% was nearly as good a cutoff point as 14%." That means that only slight differences in the study population may have resulted in a completely different cutpoint for SPF.

The wide range in the cutpoints used is an important aspect, in addition to the "interobserver variation in interpretation and different computer programs used to find S-phase," which led Sharma et al. (*17*) to conclude that "comparison between different studies where percent S-phase has been calculated is not possible." Some other important aspects, such as the problems of determining SPF on paraffin-embedded tissue or from aneuploid tumors, may have influenced the variety of cutpoints in addition to that due to the minimum *P*-value approach, but that discussion is not within the scope of this paper. The problem of standardization and the necessity of quality-control programs are discussed by Dressler (*18*).

With the following example, we will demonstrate that the minimum *P*-value approach gives different cutpoints in various subpopulations and that the *P* values associated with this approach are much too small.

Illustration Using an SPF Dataset

The database of the study consisted of all patients who had surgery for primary breast cancer between March 1982 and December 1987 at the Department of Gynecology of the University of Freiburg. Paraffin-embedded material was available for 372 patients. Some exclusion criteria (e.g., pretreated patients or history of malignancy) were defined retrospectively, which left 266 patients with a median follow-up time of 82 months for the analysis.

Eight important patient characteristics were investigated. Besides SPF, we consider here only lymph node status and ploidy status. Except for SPF in aneuploid tumors, the data are nearly complete. According to the treatment policies of the clinic and the exclusion criteria, none of the node-negative patients had adjuvant therapy after surgery, and all node-positive patients had adjuvant chemotherapy or hormonal therapy. One hundred fifteen events (39 in node-negative and 76 in node-positive; 48 in diploid and 67 in aneuploid tumors) have been observed for recurrence-free survival, which was defined as the time from surgery to the first locoregional recurrence, distant metastasis, second malignancy, or death. More details about the study can be given (Pfisterer J, Menzel D, Sauerbrei W, et al.: manuscript submitted for publication), but here we use the study for illustrative purposes and consider only recurrence-free survival time as an end point.

Table 1 shows the *P* values of the logrank test (*19,20*) for the investigation of SPF for different cutpoints used in the literature (*8-12,14-16,21-28*) for six patient populations defined by lymph node status and ploidy status. All of these, probably with the exception of the group with node-positive, aneuploid tumors (population 6), may be considered as sensible populations for the investigation of the prognostic influence of SPF. Because of the small size of the study, especially for the subgroups (populations 2-6), we have to interpret the results of our study carefully. Table 1 demonstrates that, with the exception of the least sensible population 6, SPF seems to have no prognostic influence on recurrence-free survival using the cutpoints listed. Nevertheless, we can find for each population a cutpoint that is statistically significant at least at the 10% level and in some cases at the 1% level. In the upper part of Table 2, we have summarized the optimal cutpoints derived by the minimum *P*-value approach in the six populations of the Freiburg DNA breast cancer study. For nearly all of our populations, we find a different optimal cutpoint, and this cutpoint is usually different from any of the

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Table 1. Cutpoints for SPF used in the literature and *P* values for different patient populations in the Freiburg DNA breast cancer study

Cutpoint	Investigators, y (ref. No.)	Method	Population 1, all*	Population 2, diploid†	Population 3, node negative‡	Population 4, node positive§	Population 5, node positive, diploid‖	Population 6, node positive, aneuploid¶
2.6	Dressler et al., 1988 (*21*)	Median	.369	.338	.459	.953	.704	.333
3.0	Fisher et al., 1991 (*8*)	Median	.479	.520	.485	.928	.805	.692
4.0	Hatschek et al., 1990 (*22*)	#	.108	.181	.572	.135	.307	.170
5.0	Arnerloev et al., 1990 (*10*)	Not given	.178	.272	.884	.129	.403	**.094**
6.0	Hatschek et al., 1989 (*23*)	Median	.160	.232	.920	**.088**	.381	.115
6.7	Clark et al., 1989 (*12*)	"Optimal"	.170	.280	.884	.104	.565	**.084**
7.0	Baak et al., 1991 (*24*)	Not given	.345	.452	.670	.133	.836	**.066**
7.1	O'Reilly et al., 1990 (*15*)	Median	.540	.566	.330	.158	.836	**.091**
7.3	Ewers et al., 1992 (*25*)	Median	.540	.566	.330	.158	.836	**.091**
7.5	Sigurdsson et al., 1990 (*9*)	Median	.739	.860	.330	.232	.802	**.074**
8.0	Kute et al., 1990 (*11*)	Median	.524	.996	.407	.106	.719	**.023**
9.0	Witzig et al., 1993 (*26*)	Median	.999	.852	.838	**.044**	.962	**.023**
10.0	O'Reilly et al., 1990 (*14*)	"Optimal"	.483	.581	.164	**.012**	.962	**.006**
10.3	Dressler et al., 1988 (*21*)	Median	.316	.581	.229	**.012**	.962	**.006**
12.0	Sigurdsson et al., 1990 (*9*)	"Optimal"	.603	.613	.463	.144	.994	**.060**
12.3	Witzig et al., 1993 (*26*)	**	.755	.631	.406	.133	.994	**.047**
12.5	Muss et al., 1989 (*27*)	Median	.911	.631	.463	.233	.994	**.094**
14.0	Joensuu et al., 1990 (*16*)	"Optimal"	.616	.835	.490	.953	.994	.736
15.0	Joensuu and Toikkanen, 1991 (*28*)	"Optimal"	.220	.835	.490	.352	.994	.530

*207 patients; 83 events.
†119 patients; 47 events.
‡98 patients; 27 events.
§109 patients; 56 events. All *P* values <.1 shown in bold.
‖59 patients; 31 events.
¶50 patients; 25 events. All *P* values <.1 shown in bold.
#Three groups with approximately equal size.
**Upper third of SPF distribution.

cutpoints considered so far. The corrected *P* values shown in the lower part of Table 2 are discussed below.

For the node-positive patients (population 4), we show a typical graph of the dependence of the *P* value of the logrank test statistic on the cutpoint (Fig. 1). The *P*-value plot demonstrates the instability of the minimum *P*-value approach and shows that only minor differences in the value of the logrank statistic and its corresponding *P* value may lead to different cutpoints that are far away from each other. The "optimal" cutpoints around 10% are only slightly better than a cutpoint around 5.5% from this point of view.

Underlying Statistical Considerations

The minimum *P*-value approach requires the systematic variation of the cutpoint when categorizing a continuous covariate like SPF and computing a *P* value for each cutpoint. This approach clearly leads to a serious problem of multiple testing (*29*). When a series of statistical tests, each with a prespecified nominal type I error rate (α) of, for example, 5%, is performed on the same data, then this procedure leads to a global error rate for the whole procedure that might be much higher than 5%. In this particular problem, the different test statistics involved (as illustrated in Fig. 1) are not independent so that the well-known Bonferroni correction is not adequate, at least for a larger number of hypothetical cutpoints. Theoretical arguments (*5,6*) and results from simulation studies (*30*) demonstrate that the false-positive rate can be inflated to values exceeding 40% when a nominal level of 5% is used.

All of the studies cited in Table 1 used the logrank test. Fig. 2 shows the false-positive rate of the logrank test (*19,20*), i.e., the probability of obtaining a significant result at the 10%, 5%, and

Table 2. Optimal cutpoints derived by the minimum *P*-value approach in the Freiburg DNA breast cancer study*

	Population 1, all (n = 207)	Population 2, diploid (n = 119)	Population 3, node negative (n = 98)	Population 4, node positive (n = 109)	Population 5, node positive, diploid (n = 59)	Population 6, node positive, aneuploid (n = 50)
Optimal cutpoint	5.4	5.4	9.0-9.1	10.7-10.9	3.7	10.7-11.2
P value	.037	.051	.084	.007	.068	.003
Relative risk using optimal cutpoint	1.58	1.87	0.28	2.37	1.94	3.30
95% confidence interval	1.03, 2.44	1.00, 3.49	0.07, 1.19	1.27, 4.44	0.95, 3.96	1.49, 7.29
Corrected *P* value	.403	>.5	>.5	.123	>.5	.063
P value from Cox model	.340	.276	>.5	.061	>.5	.031

*Estimated relative risks with 95% confidence intervals (upper part); corrected *P* values (for explanation *see* text) and *P* values from a Cox model including SPF as a continuous covariate (lower part). n = number of patients.

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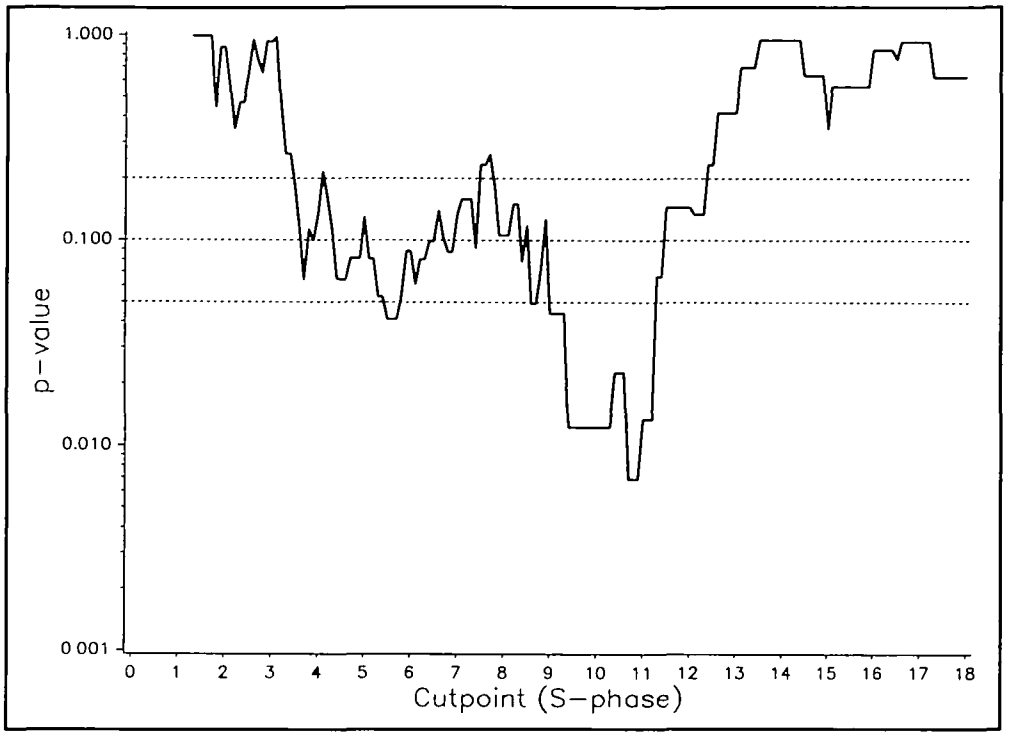

Fig. 1. *P* value of the standardized logrank statistic as a function of the cutpoint used for SPF in the Freiburg DNA breast cancer data (population 4: lymph node-positive patients).

1% levels when there is no effect of the prognostic factor at all, dependent on the sample size, for selection intervals with 80% and 90% of values of the prognostic factor considered as cutpoints. It can be seen that there is hardly any dependence on sample size, but there is an increase in the false-positive rate when the percentage of values of the prognostic factor that are considered as potential cutpoints is increased. These simulation results confirm that the minimum *P*-value approach yields a significant result ($P<.05$), with a probability of around 40% for a factor that has no prognostic relevance at all. This fact is overlooked by most of the investigators who have used this approach in analyzing the SPF or other prognostic factors in breast cancer.

The theoretical considerations mentioned above (*5,6*) allow a correction, valid for large sample sizes, of the minimal *P* value to allow for the multiple testing, leading to a true false-positive rate of 5%, for example. If P_{min} denotes the minimum *P* value of the logrank statistic, the corrected *P* value, P_{cor}, can be obtained as follows:

$$P_{cor} = \varphi(z)\,[z - (1/z)]\,\log_e[(1-\varepsilon)^2/\varepsilon^2] + 4\,\varphi(z)/z,$$

where φ denotes the probability density function and z is the $(1 - P_{min}/2)$-quantile of the standard normal distribution. The selection interval is characterized by the proportion ε of smallest

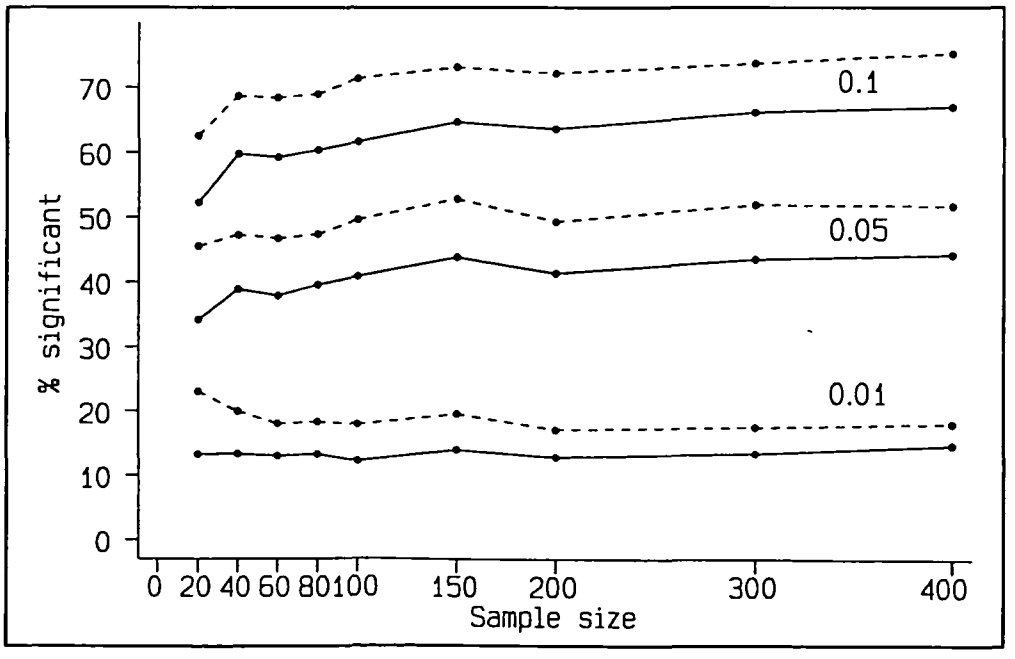

Fig. 2. Effect of the selection interval on the false-positive rate of the minimum *P*-value approach for $\varepsilon = 0.1$ (solid) and $\varepsilon = 0.05$ (dashed), for nominal levels of 10%, 5%, and 1%. The selection interval is characterized by the proportion ε of smallest and largest values that are not considered as potential cutpoints. Each plotted point was obtained from 2000 simulated samples based on there being no relation between the covariate and survival, with no censoring of survival time.

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and of largest values of the prognostic factor that are not considered as potential cutpoints.

Therefore, as an example, the minimum P value in our full dataset (see population 1 in Table 2) is equal to .037 when 5.4 is used as a cutpoint, so that $(1 - P_{min}/2) = .982$. From a table of the standard normal distribution, we find that the .982 - quantile is $z = 2.08$. The probability density function of the standard normal distribution φ evaluated at $z = 2.08$ is .045. If $\varepsilon = 10\%$, then the selection interval is defined by excluding the 10% smallest and 10% largest values of SPF as possible cutpoints, and we get $\log_e [(0.9/0.1)^2] = 4.394$. Thus, we get for the corrected P value

$$P_{cor} = .045 \cdot 1.599 \cdot 4.394 + .087 = .403,$$

a value far from being statistically significant.

One can derive from the above formula, for example, that a value of about $P_{min} = .002$ corresponds to $P_{cor} = .05$, when $\varepsilon = 10\%$. Similarly, for $\varepsilon = 5\%$, a value of $P_{min} = .001$ corresponds to $P_{cor} = .05$. These figures can be used as a very rough check whether or not a result obtained by the minimum P-value approach is statistically significant. Although the formula above can be used on a pocket calculator, it involves the evaluation of the probability density function of a standard normal distribution. Instead, one can use the simple approximations

$$P_{cor} \approx -1.63\, P_{min}\,(1 + 2.35 \log_e P_{min}) \text{ for } \varepsilon = 10\% \text{ and}$$
$$P_{cor} = -3.13\, P_{min}\,(1 + 1.65 \log_e P_{min}) \text{ for } \varepsilon = 5\%,$$

which are nearly identical to the formula above for small minimum P values ($.0001 < P_{min} < .1$) and can be obtained very easily. In our example calculation, we get $P_{cor} = -1.63 \cdot .037\,[1 + 2.35 \log_e(.037)] = .407$, which is nearly identical to the value already obtained. When applying the correction formula to the minimal P values obtained for the "optimal" cutpoints in the six populations in the Freiburg DNA breast cancer data using again a selection interval that excludes the 10% smallest and 10% largest values of SPF, we obtain corrected P values, all exceeding the 5% level (lower part of Table 2). Thus, none of the "optimal" cutpoints turns out to be significant in these data.

Discussion

In this commentary, we have addressed the problem of categorizing a continuous prognostic factor and have considered in particular the use of a data-dependent "optimal" cutpoint. The literature on the role of SPF in breast cancer highlights this problem, since there have been so many proposed cutpoints that cannot all be "optimal." As a result, a comparison between different studies is nearly impossible and the role of SPF still remains a controversial issue. The prognostic value of SPF can be assessed only in sufficiently large studies where the other important prognostic factors are simultaneously considered in an adequate multivariate analysis.

We have shown the consequences of a naive and uncritical use of the minimum P-value method that could lead to about a 10-fold increase in the false-positive rate. To examine if a prognostic factor has any influence on disease-free or absolute survival, the P value has to be adjusted using the formula presented. None of the cited papers that used this method adjusted their P value. In addition, it should be kept in mind that the cutpoint obtained is highly data dependent and so would be expected to vary markedly between samples.

Another important problem associated with the minimum P-value approach concerns the estimation of the effect of the prognostic factor. Although we are able to correct the P value, the effect is generally considerably overestimated. To give a drastic example, using the minimum P-value approach, Jänicke et al. (*31*) obtained a cutpoint of 2.6 ng/mg protein associated with a relative risk of 21.1 for the urokinase-type plasminogen activator antigen as a predictor of early relapse in breast cancer. In an updated analysis of the original data set with additional follow-up time and new patients having entered the study (*32*), this relative risk has been reduced to about 3, which seems to be much closer to a realistic value. In any study, we cannot know by how much the effect has been overestimated and no correction is possible.

Many investigators who report the derivation of an "optimal cutpoint" then include the marker as a binary variable in a Cox multiple regression analysis (*33*). Because of the method of selecting the cutpoint, this variable will have an inflated effect in the Cox analysis as well and may thus be included in the final model at the expense of other variables that are really more important. A key aspect of the evaluation of a new marker is whether it provides additional information after recognized prognostic factors have been considered (*2*). Similar comments apply to studies of other markers in breast cancer, such as nm23 (*34*) and cathepsin D (*35*), as well as in other cancers (*36-38*).

Most researchers seem to feel that it is desirable to split patients into low-risk and high-risk groups. While there can be clinical value in such a dichotomization, there are two serious weaknesses of the analysis as usually performed. First, if the median or some other prespecified cutpoint is used, there is considerable loss of information; thus, the probability of failing to detect a real association is increased. To some extent the same applies to the corrected P value after the minimum P-value approach. Second, risk groups should ideally be defined after allowing for other known prognostic variables. Groups constructed from one variable will each contain a mixture of patients with and without the other risk factors. If there is an association between the variable of interest and another important prognostic variable, the "optimal" cutpoint may reflect this interrelationship. For example, there is a marked difference in SPF between diploid and aneuploid tumors (*14*), and the optimal cutpoint for SPF in a logrank test may well reflect just the best value for discriminating between these two ploidy categories. Prognostic groups can be more sensibly constructed using all variables found to be significant in a regression model. If, on the other hand, the aim is to see whether a variable is prognostic, another possibility would be not to categorize the variable at all (*39*).

For the Freiburg DNA breast cancer study, we have also analyzed the data by treating SPF as a continuous covariate in a Cox regression model (*33*), with no other variables in the model. The P values obtained are shown in Table 2 and are not too different from the corrected values from the minimal P-value approach in all six populations considered. In contrast to the abrupt change implicitly modeled in the cutpoint approach, this

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type of analysis relies on the assumption of a linear relationship between the prognostic factor and the logarithm of the relative risk, although nonlinear relationships can also be modeled. However, the null hypothesis that there is no effect of the prognostic factor on survival is identical in both approaches. In a given situation, the question of whether such a model-based approach or a cutpoint approach—preferably with a small number of prespecified cutpoints—depends on the data given and their distribution as well as on the specific aims of the study and needs careful consideration (*40*). It is notable that all of the published studies on SPF (Table 1) used some form of categorization. The true relation between the variable and risk may not be linear, but it is almost certainly smooth. If groups are to be constructed, it might, therefore, be more reasonable to have three or more groups, to get a better idea of how risk varies. Restriction on the investigation of a few prespecified possible values for a cutpoint might be considered preferable to a single cutpoint, however chosen. In the case of a small number of prespecified cutpoints, a correction formula based on a modified Bonferroni method (*41,42*) can be used.

In this commentary, we have focused on one particular issue in the evaluation of prognostic markers. There are many other general issues that need to be considered as well (*43*); these issues are reviewed by Simon and Altman (*2*).

In summary, we recommend that authors investigating the prognostic value of new markers use prespecified cutpoints, preferably three or four rather than just two. If possible, the choice of the cutpoints should be guided by biological reasoning, knowledge of measurement techniques, and simplicity. We think that the so-called "optimal" cutpoint approach should not be used. If it is used, the *P* value must be corrected and investigators should acknowledge the possible bias in the estimated effect on survival. Also, the term "optimal" should be abandoned, and the method should be referred to as the minimum *P*-value method. It is desirable for investigators to report a univariate Cox regression analysis with the marker treated as continuous, even when an analysis using categories is also reported. This approach will improve the ability to compare directly results from different studies. If a Cox multiple regression analysis is performed, investigators should examine whether the new marker provides independent prognostic information in addition to recognized prognostic factors.

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Notes

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