Prognosis Versus Actual Outcome. IV. The Effectiveness of Clinical Parameters and IL-1 Genotype in Accurately Predicting Prognoses and Tooth Survival

Michael K. McGuire* and Martha E. Nunn†

Background: Recently, a genetic marker (IL-1 genotype) that identifies individuals at higher risk for developing severe periodontal disease was discovered. A subgroup of the population reported on earlier was evaluated to determine if knowledge of the patient's IL-1 genotype would improve accuracy in assignment of prognoses and prediction of tooth loss.

Methods: This subgroup consisted of 42 patients (1,044 teeth) in maintenance care for 14 years; 16 tested IL-1 genotype-positive (IL-1GP). Nine were smokers, and 30 had a history of smoking, with an average of 29.44 pack years. A multiple Cox regression model and Kaplan-Meier survival plots were fit to the subset of patients to evaluate tooth loss.

Results: Both IL-1GP and heavy smoking were significantly related to tooth loss. A positive IL-1 genotype increased the risk of tooth loss by 2.7 times, and heavy smoking by 2.9 times. The combined effect of IL-1GP and heavy smoking increased the risk of tooth loss by 7.7 times. The value of clinical parameters traditionally used to assign prognosis was found to be dependent on IL-1 genotype and smoking status. In the model that included IL-1 genotype and heavy smoking, none of the clinical parameters added significantly to the model for tooth loss while mobility, probing depth, crown-to-root ratio, and percent bone loss added significantly to the model, which included IL-1 genotype in non-smokers. IL-1GP patients and patients who smoked heavily demonstrated a much worse tooth survival rate when compared to IL-1 genotype-negative patients and non-smokers, respectively.

Conclusions: Knowledge of the patient's IL-1 genotype and smoking status will improve the clinician's ability to accurately assign prognosis and predict tooth survival. Clinical implications are as follows. Investigators were unable to judge which patients would be IL-GP or negative based on their clinical presentation or family history of tooth loss due to periodontal disease. Since periodontal diseases are multifactorial, knowledge of the patient's genotype is more important in predicting future risk than explaining past disease. Knowledge of IL-1 genotype status would be important in developing a treatment plan and predicting tooth survival for a new patient who smokes and presents with periodontal disease, especially if restorative care is needed. Knowledge of a maintenance patient's IL-1 status would help target therapy for non-responding areas; one would be less likely to take a "wait and see approach" with IL-1GP patients. IL-1 positive non-smokers can be successfully treated and maintained over long periods of time. *J Periodontol 1999;70: 49-56.*

KEY WORDS

Periodontol diseases/diagnosis; prognosis; genotype, IL-1; forecasting; risk factors; smoking/adverse effects; tooth loss/etiology; tooth loss/prevention and control; outcome assessment.

*Private practice, Houston, TX; Department of Periodontics, University of Texas, Dental Branch Houston and Health Science Center at San Antonio.
†Department of Public Health Sciences, Baylor College of Dentistry, Dallas, TX.

Identification of one or more commonly taught clinical parameters (Table 1) as they uniquely apply to the tooth is the traditional method of assigning prognosis and predicting tooth survival. These parameters are recorded and weighed according to past clinical experience, and a prognosis is assigned. Previous studies in this series of papers [1-3] have evaluated this method for assigning prognosis and predicting tooth survival and have concluded that there is a relationship between prognosis and tooth loss. Teeth with a worse prognosis had a worse survival rate, but the clinical parameters commonly taught to assign prognosis did not adequately explain that connection. There is a relationship, but there is more to it than we currently know.

One of the underlying premises of this series of papers is that the traditional process for assigning prognosis was created from an outdated model of disease progression, which was based on the assumption that all plaque is the same and everyone is equally susceptible. Today, even though it is recognized that there are important differences in the microbial composition of plaque, it is assumed, for clinical decision making, that regardless of the composition, all

Table 1.

Parameters Used in Assigning Prognosis

Individual tooth prognosis
Percentage of bone loss
Probing depth
Distribution and type of bone loss
Presence and severity of furcations
Mobility
Crown-to-root ratio
Root form
Pulpal involvement
Caries
Tooth position and occlusal relationship
Strategic value
Therapist knowledge and skill
Overall prognosis
Age
Medical status
Individual tooth prognosis
Rate of progression
Patient cooperation
Economic consideration
Knowledge and ability of dentist
Etiological factors
Oral habits and compulsions

plaques do the same thing to the patient. Similarly, it is assumed that patients respond in a uniform manner to any kind of plaque. The profession abandoned that disease concept years ago, but we continue to use it as the basis for the traditional method to assign prognosis.

Recently, a specific genotype of the polymorphic interleukin-1 (IL-1) gene cluster has been identified.[4] This report demonstrated that a specific genetic marker identified adults who, with a bacterial challenge, were much more likely to have severe periodontitis. The purpose of this study is to determine if knowledge of the patient's IL-1 genotype will improve the clinician's accuracy in assigning prognoses and predicting tooth loss.

MATERIALS AND METHODS

As reported earlier, 100 consecutive patients with at least 5 years of maintenance care were selected from one clinician's appointment book over a 2-month period. All had been initially diagnosed as having chronic, generalized moderate to severe adult periodontitis and were treated by the same clinician. The inception cohort (study group) was established at a fairly uniform point in their disease, and all patients followed a similar course of treatment. Patients in this study were in maintenance treatment regimens of 2- or 3-month intervals. The majority of the patients were compliant and demonstrated fair oral hygiene. Additional information regarding the study population, therapy, limitations of the study, and assignment of prognoses can be found in the initial reports.[1-3]

Of the original 100 patients in the prognosis population, 52 were available for reevaluation. Forty-five of the 52 were Caucasian. Because the Kornman et al. study[4] limited their population to northern European Caucasians and because the majority of our subgroup was Caucasian, a decision was made to limit our study population to Caucasians as well. Forty-two of the 45 Caucasians were ultimately reevaluated and tested[‡] for the IL-1 genotype. Of the remaining 3 Caucasians, one had suffered a stroke and the other 2 declined to participate.

Within a protocol approved by an institutional review board, subjects signed a consent form after being advised of the nature of the study. The dental and medical history, which included a more detailed smoking history, was updated, and a full-mouth periapical radiographic survey was made on each patient. There were 30 women and 12 men in the prognosis/IL-1 subset. The average age of the patient at initial examination was 46 years, with a range between 33 and 62 years. The frequency distributions by age at initial examination and by current age are given in Table 2. Each subject's finger was cleaned with an antiseptic wipe, and the skin was punctured with a sterile lancet. Fingerstick blood samples were collected on a DNAase-free blotting paper and analyzed blind at a commercial laboratory under contract to Medical Science Systems (Flagstaff, AZ) for the IL-1 genotype.

Table 2.

Frequency Distribution by Age

Age at Initial Examination		Current Age	
Age Range	No. Patients	Age Range	No. Patients
30-39	9	30-39	0
40-49	19	40-49	5
50-59	12	50-59	16
60-69	2	60-69	13
70-79	0	70-79	8

Statistical Methods

Statistical analysis was performed using SAS[§] and S-plus[‖] statistical software packages. The primary analysis utilized multivariate survival analysis with an

[‡]PST, Medical Science Systems, Flagstaff, AZ.
[§]SAS Institute, Cary, NC.
[‖]Statistical Sciences, Inc., Seattle, WA.

SAS macro written by Bergstralh, Kosanke, and Therneau.[5] Robust log rank tests were conducted on each clinical variable individually to determine its effect on tooth loss over time. To assess the effect of a positive genotype in the presence of other clinical parameters, a multivariate Cox proportional hazards regression model was constructed.

The general form of a Cox proportional hazards regression model is given by the following equation:

$$\lambda(t)=\lambda_{\circ}(t)\ \exp(ßx)$$

where ß is a vector of regression coefficients corresponding to a vector of values given by x. The $\lambda_{\circ}(t)$ term corresponds to the "baseline" hazard (i.e., the hazard when x is a vector of zeroes). The hazard refers to the instantaneous probability of failure, given that a tooth has survived to that point. The term exp(ßx) gives the relative risk, which corresponds to the multiplicative increase (or decrease) in baseline hazard for given values of x. The relative risk obtained from a Cox regression model takes into account the time until a tooth is lost, unlike the results obtained directly from a simple contingency table. Teeth that survived for more years are treated differently from those that last only a short time after entry into the study. This adjustment is important, because if one did not adjust for time until a tooth was lost, a tooth that was lost 6 months into the study would be equivalent to a tooth lost 12 years into the study. Clearly, that could lead to false conclusions.

In addition to fitting Cox regression models, Kaplan-Meier plots for survival were also constructed. These plots depict the estimated tooth survival probabilities over time according to group.

Using these statistical methods, an exploratory analysis was carried out initially on all data to determine areas that may yield significant results. These areas were then thoroughly evaluated using more sophisticated statistical approaches.

RESULTS

Exploratory Analysis

Forty-eight teeth out of 1,044 teeth that were in this subset of patients when the study began were lost. Of the 48 teeth that were lost, 47 were lost as a result of periodontal disease. The one tooth that was not lost due to periodontal disease (a root fracture) was excluded from this analysis so that 47 lost teeth out of 1,043 were included for analysis. Table 3 contains summary statistics on some initial clinical parameters for lost teeth and surviving teeth.

The number of current smokers in the subset of 42 subjects was 9. Thirty of the 42 subjects had a history of having smoked at one time. Twenty-two patients were smokers when they were initially treated for periodontal disease. Of those patients who had a history of smoking, the average number of pack years (packs [20 cigarettes per pack] of cigarettes smoked per day times the number of years smoked) was 29.44 (range: 2.5–90). Of the 42 patients in the study, 16 tested positive for the composite genotype. Of those testing positive for the composite genotype, 10 were women and 6 were men. There were 1,044 teeth in these 42 patients initially. Of the 47 periodontally involved teeth that were lost, 27 (out of 386 teeth in these patients) were in IL-1 genotype-positive patients. The average time from entry into the study until tooth loss was 7.11

Table 3.

Clinical Characteristics

	Lost Teeth (n=47)					Surviving Teeth (n=996)				
Clinical Parameter	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum
Probing depth	7.11	2.01	7.0	3.0	10.0	4.74	1.99	5.0	3.0	10.0
Furcation	1.11	1.11	1.0	0.0	3.0	0.24	0.62	0.0	0.0	3.0
Furcation=1 (%)	17.0					8.1				
Furcation=2 (%)	27.7					5.2				
Furcation=3 (%)	12.8					1.7				
Mobility	0.79	1.12	0.0	0.0	3.0	0.08	0.37	0.0	0.0	3.0
Mobility=1 (%)	4.3					3.0				
Mobility=2 (%)	21.4					1.7				
Mobility=3 (%)	4.6					0.5				
Bone loss (%)	41.2	17.2	50	10	75	34.7	15.1	25	10	75
Crown-to-root ratio (%)	48.9					16.9				
Positive genotype (%)	57.5					34.4				

years (range: 1-12.33 years). Table 4 shows the distribution of initial prognosis for teeth in genotype-positive and genotype-negative patients.

To further investigate which factors significantly affected tooth loss in this subset, a series of log rank tests was carried out using the robust test for correlated data. Log rank tests are used to evaluate survival data to determine if there is a difference in survival rate over time when the tooth is under the influence of a particular variable. Factors considered for analysis included genotype (positive or negative for the composite genotype), compliance, oral hygiene, smoking history (heavy smokers vs. light smokers or non-smokers), probing depth, furcation involvement, mobility, crown-to-root ratio, root form, parafunctional habit (with and without splint), and initial prognosis. Table 5 shows those factors that were found to be at least marginally related to tooth loss for this subset of patients (P<0.10).

Table 4.

Initial Prognosis by Genotype Status*

Initial Prognosis	Genotype-Negative	Genotype-Positive
Good	443 (67.4%)	226 (58.5%)
Fair	149 (22.7%)	123 (31.9%)
Poor	55 (8.4%)	29 (7.5%)
Questionable	7 (1.0%)	8 (2.1%)
Hopeless	3 (0.5%)	0 (0.0%)

* Initial prognosis based on assignment method as defined by McGuire.[1]

Table 5.

Log Rank Tests of Significant Clinical Parameters on Survival of Teeth

Variable	P Value	Risk Ratio
Genotype	0.011	2.59
Smoking (in pack years)	0.062	1.02
Heavy smoking	0.074	2.73
Probing depth	<0.001	1.47
Furcation (0,1,2,3)	0.004	1.81
Mobility (0,1,2,3)	<0.001	3.44
Crown-to-root ratio (0 or 1)	<0.001	3.59
Initial prognosis		
Fair or poor	0.003	3.20
Questionable or hopeless	<0.001	30.82

It should be noted that both patient compliance and hygiene were tested, but both of these factors failed to be statistically significant. Those testing positive for the composite gene had an unadjusted increased risk of tooth loss of 2.59 (P=0.01). Smoking history was also evaluated to determine the relationship of smoking to tooth loss. A more detailed account of each subject's smoking history permitted a better assessment of the effect of smoking on tooth loss due to periodontal disease. Since the effects of smoking are thought to be dose related, packs of cigarettes per day times the number of years the patient smoked were used to evaluate the relationship to tooth loss. The risk ratio for one pack year of smoking was 1.02 (P=0.062) and was only marginally related to tooth loss for this subset. To quantify this risk ratio for smoking, if one smoked 2 packs of cigarettes per day for 20 years, the unadjusted risk of tooth loss would be double that for someone who had never smoked. In addition to looking at the effect of smoking measured in pack years on tooth loss, we also investigated the relationship of heavy smoking on tooth loss. Heavy smoking was defined as 40 pack years or greater. Heavy smoking did not reach statistical significance, with an unadjusted risk ratio of 2.73 (P=0.074).

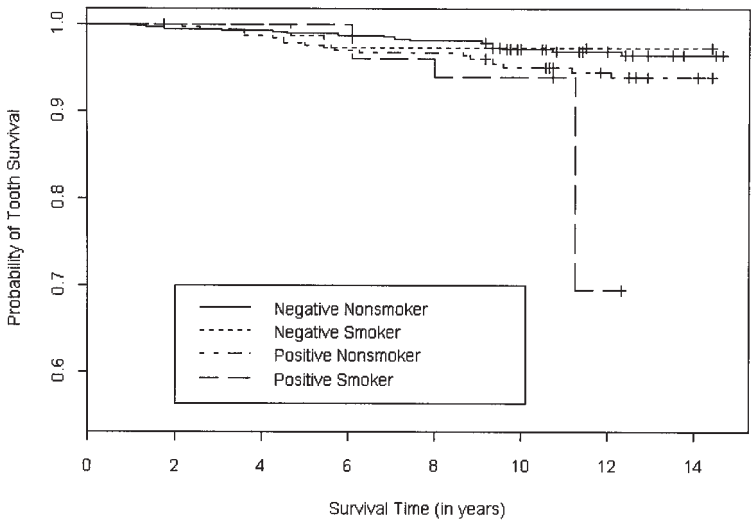
Regression Analysis

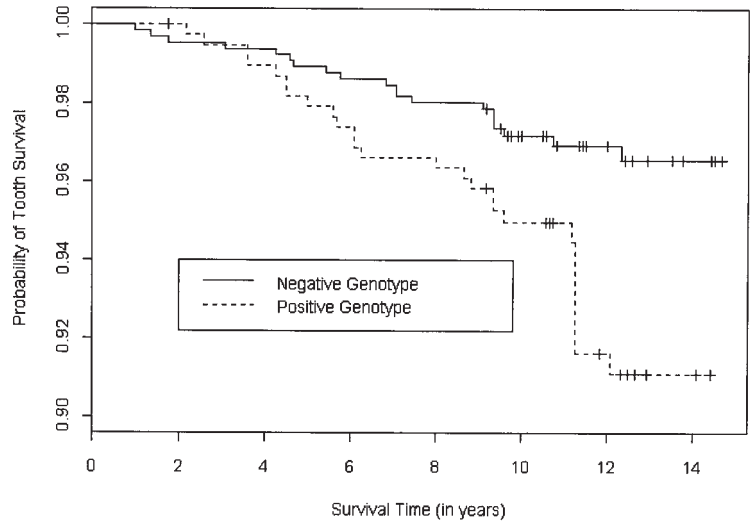
A multiple Cox regression model was fit to the subset of patients in this study. This analysis evaluates the impact of the different variables simultaneously (taken together as a group) as they relate to tooth loss. Variables entered initially were heavy smoking (≥ 40 pack years) and genotype. Since both factors are thought to be promoters of periodontal disease, it seemed logical to include these 2 parameters initially as they are likely to be correlated with other clinical measures of periodontal disease which are merely surrogate markers for the progression of disease, such as mobility, bone loss, etc. The Cox regression model that included heavy smoking and genotype is provided in Table 6. In addition, a Kaplan-Meier survival plot of genotype and heavy smoking was constructed and is given in Figure 1 (top). This plot shows that IL-1 genotype-positive, heavy smokers demonstrated a substantial drop in tooth survival at around 11 years when compared to the other groups. Effect modification (interaction) for heavy smoking on positive genotype was investigated but was not statistically significant. Kaplan-Meier survival plots for genotype and heavy smoking individually were also constructed and are shown in Figure 1 (middle and bottom). Both a positive genotype and heavy smoking were found to be significantly related to tooth loss. A positive genotype increased the risk of

Table 6.

Cox Regression Model for Heavy Smoking and Genotype

Parameter	Estimate	P Value	Risk Ratio
Positive genotype	0.98	0.011	2.66
Heavy smoking	1.06	0.040	2.88





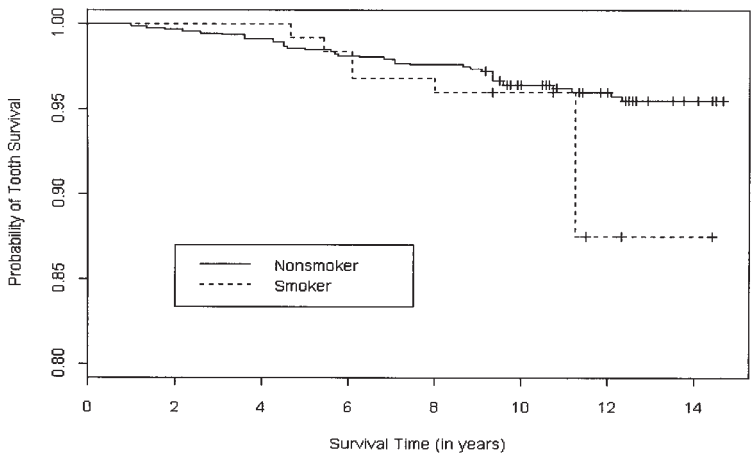


Figure 1. *(Top) Survival plot for heavy smoking and positive genotype. (Middle) Survival plot for positive genotype. (Bottom) Survival plot for heavy smoking.*

tooth loss from periodontal disease by 2.66, while heavy smoking increased the risk of tooth loss from periodontal disease by 2.88. Each of the clinical parameters was added to the original model that included heavy smoking and positive genotype. No clinical parameter was found to add significant information to the model that had heavy smoking and genotype. Probing depth, mobility, and furcation involvement were all statistically significant in the model when added individually to the model which included only genotype, but each of these clinical factors masked the effect of heavy smoking. In other words, the presence of each of these clinical parameters made the effect of heavy smoking statistically insignificant. This masking results from these clinical parameters being in the "causal pathway"; i.e., heavy smoking leads to deeper probing depths, greater mobility, and greater furcation involvement which, in turn, leads to an increased risk of tooth loss. When both positive genotype and heavy smoking are present simultaneously, their odds ratios are multiplicative. The combined effect of a positive IL-1 genotype and heavy smoking increases the risk of tooth loss by 7.7 times.

In addition, indicator variables for initial prognosis were added to genotype and heavy smoking, and these also masked the heavy smoking effect. When heavy smoking was eliminated from the model, several of the initial clinical parameters were significant with posi-

Table 7.

Cox Regression Models for Genotype With Initial Clinical Parameters Individually

Parameter	Estimate	*P* Value	Risk Ratio
Positive genotype	0.70	0.087	2.02
Fair or poor	1.00	0.021	2.72
Questionable or hopeless	3.25	<0.001	25.71
Positive genotype	0.85	0.028	2.33
Furcation (0,1,2,3)	0.52	0.013	1.68
Positive genotype	0.94	0.007	2.57
Mobility (0,1,2,3)	1.23	<0.001	3.41
Positive genotype	0.90	0.019	2.45
Probing depth	0.38	<0.001	1.47
Positive genotype	0.95	0.012	2.59
Crown-to-root ratio (0,1)	1.27	<0.001	3.55
Positive genotype	0.93	0.009	2.52
Bone loss	0.90	0.011	2.47

tive genotype included. Initial prognosis, mobility, furcation involvement, probing depth, and crown-to-root ratio were all significant factors when added to positive genotype individually (Table 7). Effect modification for each of these clinical factors was also investigated, but none of them yielded significant results. Compliance, oral hygiene, and the presence of a parafunctional habit without a splint were all insignificant when included individually with positive genotype.

A Kaplan-Meier survival plot was constructed to demonstrate the tooth survival for non-smoking, IL-1 genotype-positive patients versus non-smoking, and IL-1 genotype-negative patients and is shown in Figure 2. As seen in the plot, the vast majority of teeth in this subset survived.

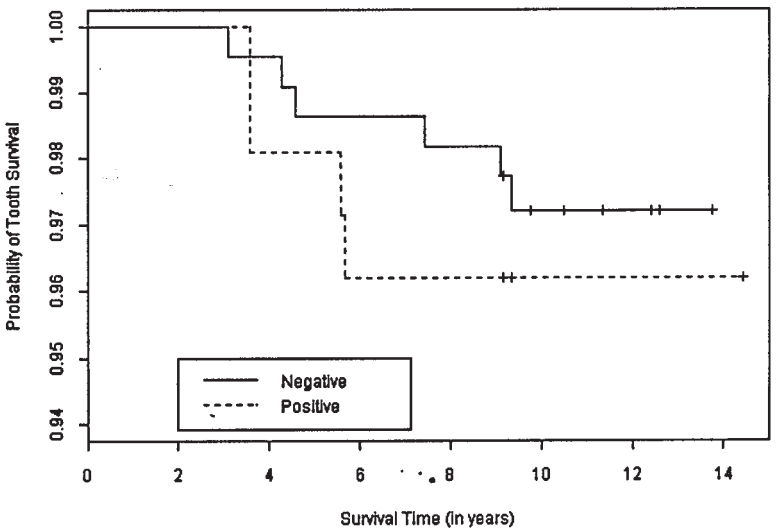


Figure 2.
Survival plot of genotype-positive vs. genotype-negative non-smoking patients.

DISCUSSION

In the previous series of papers,[1-3] the authors explored the relationship of various clinical parameters used in the assignment of prognosis to tooth loss. It was concluded that a relationship exists between tooth loss and prognosis, but the exact nature and description of that relationship were unclear. In particular, it was suggested that the present system for assignment of prognosis should be revised to include other prognostic factors that are found to be significantly related to tooth loss. Studies have demonstrated that the presence of bacteria alone will not explain periodontal disease progression.[6] Our previous papers[1-3] demonstrated that environmental and anatomical factors could not predict disease outcome. Perhaps the missing link was the individual's genetic background. The purpose of this study therefore was to determine if the investigator's knowledge of the patient's IL-1 genotype would improve the accuracy of the traditional method of assigning prognoses and predicting tooth loss.

Kornman et al.[4] estimated that approximately 30% of the population will be IL-1 genotype-positive. Sixteen of the 42 patients (38%) in our subgroup tested IL-1 genotype-positive, slightly higher than, but closely correlating with, their projection of 30%. Prior to testing, the authors thought that the percentage of IL-1 genotype-positive individuals in this subgroup might be much greater than 30% because of referral bias. It would be logical to assume that a population drawn from a periodontal practice might have considerably more IL-1 genotype-positive individuals than the general population. Reasons that this did not occur might include the relatively small size of our subset and the fact that some of the IL-1 genotype-positive individuals experienced disease so severe that their teeth were lost before they ever reached a periodontist.

Clinically important was the fact that the investigators were unable to judge which patient would be IL-1 genotype positive or negative based on their clinical presentation or family history of tooth loss due to periodontal disease. Table 4 segregates initial prognosis by genotype status. Initial prognosis was determined by the tooth's clinical presentation, and as can be seen in the table, there is little correlation between the condition of the tooth and whether the patient was genotype negative or positive. Although this lack of correlation seems contradictory to the findings that the IL-1 genotype is associated with more severe disease, this observation may actually reveal a critical concept relative to practical interpretation of risk factors. Since patients may reach moderate to severe disease due to multiple factors, the initial clinical presentation may be only partially related to the genetic influences.[7,8] The clinical state at initial presentation is undoubtedly an accumulation of multiple past risk factors. The risk for future disease progression, however, will obviously be related only to present or unchangeable risk factors, such as genetics. This phenomenon is likely to make the genotype influence much greater in predicting future risk than in explaining past disease history.

Table 8 indicates that, at least in our subgroup, there was no correlation between IL-1 status and family history of periodontal disease. The reliability of this lack of correlation is not known due to its reliance on the unconfirmed

Table 8.

Comparison of IL-1 Status and Family History of Tooth Loss Due to Periodontal Disease

IL-1	Family History	N
-	-	12
-	+	14
+	-	9
+	+	7

recollection of the subjects and the relatively small size of the subset. Nevertheless, it is important for the clinician to keep in mind that the patient's genotype is only one element in a multifactorial disease. Bacteria cause the disease, but the individual's genetic makeup and environmental influences, such as smoking, determine how severe the disease will be. It is therefore impossible for a clinician to determine who will be IL-1 genotype positive or negative simply by looking at the patient's clinical presentation or evaluating the family history.

It should be noted that the presence of a parafunctional habit without a splint was previously shown to be related to tooth loss.[3] The lack of a significant association here is related to this subset of patients that included only a small proportion of those patients with the presence of a parafunctional habit without a splint. It should also be noted that both patient compliance and hygiene were tested (Table 5), but both of these factors failed to be significantly related to tooth loss for this subset. One reason for this is that these patients are probably more homogeneous with respect to compliance and hygiene since they are in a well-controlled maintenance group.

The Kornman et al. study[4] did not evaluate smokers in terms of genotype and disease severity because smoking was already recognized as a risk factor for periodontal disease, and they only evaluated the pure genetic effect of the IL-1 polymorphism. That is reasonable from a study design viewpoint, but we elected to include smokers because the reality of clinical practice is that many periodontal patients smoke. A more detailed smoking history than we had on the entire population was collected on the subgroup. Because the effect of smoking is thought to be dose related, we evaluated smoking in terms of pack years. Those patients with a history of smoking had an average number of pack years of 29.44 (range 2.5–90), which translates to a moderately heavy smoker. Nine of the 42 patients in the prognosis/IL-1 genotype population currently smoked. It was interesting to discover that 30 of the 42 subjects had a history of smoking at one time and 22 patients were smokers when initially treated. Clearly, there was a trend in this group to stop smoking, perhaps reflecting societal pressure and effective behavior modification as practiced in this clinical setting.

It should also be noted that the effect of smoking in the Kornman et al. study[4] was so strong that other factors were insignificant in the presence of smoking. In their study, risk factors for periodontal disease were evaluated to determine their relationship to the severity of disease. In the Kornman et al. study,[4] disease severity is a surrogate marker for the true disease outcome, tooth loss. In our study, we evaluated the relationship of risk factors for periodontal disease to tooth loss, which is the actual outcome of interest to clinicians. Ordinarily, tooth loss is not evaluated in periodontal studies because of the length of time required for follow-up and because of previous limitations on applying survival analysis to correlated data. In our study, patients were followed for 14 years so that we were able to obtain enough tooth loss to conduct survival analysis. In addition, because of the recent advances in survival analysis, we were able to adjust for the correlation between teeth in our statistical analysis. Given the difference in outcome being evaluated, it is not surprising that our results with respect to smoking differ from Kornman et al.[4]

It is interesting to note that there appears to be a high degree of collinearity between the combination of heavy smoking and a positive IL-1 genotype and baseline clinical parameters. The reason for this collinearity is probably because baseline clinical parameters such as probing depth, furcation involvement, mobility, etc. may actually be the result of heavy smoking and a positive IL-1 genotype. In other words, these baseline clinical parameters probably lie in the causal pathway (i.e., heavy smoking and a positive IL-1 genotype enhance the development of deep pockets, furcation involvement, mobility, etc. which, in turn, leads to tooth loss).

As seen in Table 6, both a positive IL-1 genotype status and heavy smoking were found to be significantly related to tooth loss. A positive IL-1 genotype increased the risk of tooth loss by 2.7 times. Heavy smoking increased the risk of tooth loss by 2.9 times. When the clinical parameters that are traditionally used to assign prognosis were added to this model, none added significantly to the model that included IL-1 genotype status and heavy smoking status. The clinical relevance of these findings is important. First, IL-1 positive genotype and heavy smoking have strong risk ratios for tooth loss. This is especially important, considering the fact that they come from a longitudinal study based on the actual outcome of tooth loss rather than from a cross-sectional study where the outcome is only a surrogate marker for the true endpoint, tooth loss. Clinically, if a new patient presents who is a heavy smoker (2.9 times more likely to lose teeth), has periodontal disease, and especially if he or she requires restorative care, the knowledge of that patient's IL-1 genotype status would be important in developing a treatment plan and predicting tooth survival. In addition, if the patient is an IL-1 genotype-positive, heavy smoker (7.7 times more likely to lose teeth), probably one of the most important treatment modalities for this high-risk patient is a smoking cessation program. Our data also indicate that the clinical parameters traditionally used in assigning prognosis in these patients do not add anything significant in the assignment of prognosis or in predicting tooth loss.

Table 7 also yields clinically relevant information. When we eliminate heavy smoking from the regression model, some of the clinical parameters combined with the positive IL-1 genotype become significantly related to tooth loss. These results indicate that for an IL-1 geno-

type-positive, non-smoking patient, it would be prudent when assigning prognosis and predicting tooth survival to weigh the following clinical parameters more heavily: mobility, furcation involvement, probing depth, percent bone loss, and crown-to-root ratio. All of the other parameters traditionally used in the assignment of prognosis were not found to be significantly related to tooth loss and are perhaps less important than we once believed.

Because we found positive genotype and heavy smoking had such high-risk ratios (2.66 and 2.88, respectively), we constructed survival plots for each variable individually. Figure 1 (middle) depicts the entire population separated by IL-1 genotype status. This plot clearly demonstrates the difference in tooth loss between the 2 categories, with the IL-1 positive-genotype patients at significantly greater risk for tooth loss. This seems to indicate that if you know nothing about the patient other than the IL-1 genotype status, you should be able to predict which patients will lose more teeth. The same can be said about heavy smoking, but the tooth loss appears to occur later, perhaps because its effect is dose related and it takes a period of time to reach a level that is clinically significant (Fig. 1, bottom).

When the 2 variables that we looked at separately in the previous survival plots are combined, we see that the IL-1 genotype-positive, heavy smokers consistently lost more teeth and demonstrated a substantial drop in tooth survival around 11 years when compared with the other groups (Fig. 1, top). Effect modification (interaction) for heavy smoking on positive genotype was investigated, but was not statistically significant. Because of the limited sample size, it is impossible to draw much inference from this lack of significant interaction term. In Figure 2, we look at survival in IL-1 positive and negative non-smokers. It is quite evident that IL-1 positive non-smokers lose more teeth over time than IL-1 negative non-smokers. But another important fact is evident from this plot. The great majority of teeth survive in IL-1 positive non-smokers even when followed over a long period of time. Clinically, this is important because it suggests that IL-1 genotype-positive non-smokers can be successfully treated and maintained, retaining the majority of their teeth for many years. Only 27 of 386 teeth were lost over 14 years in the IL-1 genotype-positive non-smokers.

This study is the first longitudinal assessment of a specific genetic influence on the deleterious outcome of periodontal disease and one of the first attempts to determine just how this new genetic information is clinically relevant. More studies will help clinicians determine precisely how knowledge of the patient's IL-1 genotype fits into clinical practice, but the summation of evidence from this study demonstrates that knowledge of a patient's IL-1 genotype status will improve the clinician's ability to accurately assign prognoses and predict tooth loss. Positive IL-1 genotype and heavy smoking increase the risk of tooth loss to periodontal disease by 2.7 and 2.9 times, respectively. The combined effect of a positive IL-1 genotype and heavy smoking increases tooth loss by 7.7 times. The value of clinical parameters traditionally used in the assignment of prognosis was found to be dependent on IL-1 genotype status and smoking status. In IL-1 genotype-positive, heavy smokers, none of the clinical parameters was significantly related to tooth loss, while initial prognosis, furcation involvement, mobility, probing depth, crown-to-root ratio, and percent bone loss were significantly related in IL-1 positive non-smokers. Finally, the results demonstrate that IL-1 genotype-positive, non-smoking patients can be successfully treated and maintained over many years.

ACKNOWLEDGMENTS

The authors would like to acknowledge Carol Knobleman, DDS and Carol Waring, RDH for their help in the operational aspects of the clinical trial. We would also like to recognize Jacquelyn Campbell, DDS for her editorial assistance with the manuscript.

Medical Science Systems, Inc., Flagstaff, Arizona, provided the genetic testing for the subjects in this study. The authors have complete control of the reporting of data and the content of this manuscript.

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Send reprint requests to: Dr. Michael K. McGuire, 3400 S. Gessner, #102, Houston, TX 77063. Fax: 713/952-0614; e-mail: mkmperio@hal-pc.org

Accepted for publication June 19, 1998.