SYSTEMS ANALYSIS

Modeling the Effect of a Disease on Culling: An Illustration of the Use of Time-Dependent Covariates for Survival Analysis

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ABSTRACT

This study demonstrated five different approaches, with and without time-dependent covariates, to determine the effect of disease on culling. It was also of interest to determine whether the time of the disease had an effect on subsequent culling (i.e., whether disease should be treated as a time-dependent covariate). To this purpose, five separate models were studied: Models 1 through 4 were Cox proportional hazards models, and Model 5 was a Weibull model. Model 1 treated disease as a binary, time-independent covariate. Model 2 treated disease as a time-dependent covariate, and one change of status was assumed to occur at the time of disease. Model 3 also assumed that one change in status occurred at the time of disease, but the effect of that change was assumed to be different depending on when the disease occurred. Models 4 (Cox) and 5 (Weibull) assumed an interaction between the occurrence of disease (time of disease) and the occurrence of culling (time of culling). As an illustration, the effect of mastitis on culling was studied for 2998 Holstein dairy cows in 10 herds. Parity and previous 305-d milk yield were also included as covariates; the data were stratified by herd. For all models, mastitis was a significant factor for culling. The significance tests for the estimates from Models 4 and 5 demonstrated that the hazard of culling differed for different stages of lactation, depending on when mastitis had occurred and when its effect on culling occurred; that is, time dependence exists between time of mastitis and time of culling.

(**Key words**: survival analysis, time-dependent covariate, Cox model, Weibull model)

INTRODUCTION

Diseases affect culling of dairy cows. The timing (and severity, which is not a topic of this paper) of a disease may influence the decision of when or whether to cull a cow. Timing has two aspects: the timing of disease occurrence and the time during lactation that culling actually occurs. A culling decision may be postponed until the end of the current lactation, generally after milk yield has fallen below some arbitrary cutoff, if veterinary costs and loss of milk revenue are not too high, or the cow may be culled immediately if the disease is life-threatening or if there is little hope of recovery of milk yield.

Developed in 1972, the Cox proportional hazards model (2) has become a popular choice for the analysis of survival data. By use of the Cox model, the hazards of some event (such as culling) can be estimated for different subjects. The hazard of one subject is always proportional to that of another. For dairy research, this technique has been used to model the time from freshening to conception (7, 8, 11). Survival analysis is also an appropriate way to analyze the length of herd life. Beaudeau et al. (2) used survival analysis, which they considered to be more powerful than standard regression techniques, to study the effect of various diseases over several lactations for French Holsteins.

A drawback of many studies is that certain covariates were treated as independent of time rather than dependent on time. Cox and Oakes (4) and Kalbfleisch and Prentice (9) discussed the use of time-dependent covariates for survival analysis. The effect of a time-independent covariate on the outcome remains constant over time. For example, over a lactation, parity does not change, so parity is time-independent and has the same effect at all stages of lactation on an outcome such as culling. If the time-independent covariate is a disease, its effect on the outcome is the same both before and after occurrence of the disease, which does not make sense unless the disease occurs very early in lactation. In contrast, a time-dependent covariate can change over time. If

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disease is a time-dependent covariate, its effect is different before and after occurrence; the effect may also vary over time if the interaction is important between the disease occurrence and the stage of lactation in which culling occurs. The purpose of this study was to compare a model with a time-independent covariate for disease and models with time-dependent covariates for disease to determine whether an interaction between the time of disease and the time of culling is important. Modeling the effect of mastitis on the culling of dairy cows is used as an illustration.

MATERIALS AND METHODS

Models

The dependent variable of interest assumed here is the length of the lactation in days. A lactation can end for one of three reasons: culling (leaving the herd for any reason, such as death or sale for dairy or meat), the start of a new lactation, or the end of the study. Either of the latter two reasons results in censoring of the cow record.

The term hazard refers to the relative risk of an event (e.g., culling). For example, if two cows have hazards of 0.5 and 1.5, the latter cow is three times as likely to be culled as is the former cow (1). The hazard ratio (or relative culling risk) is 3. The proportional hazards model is used to describe the hazard (or instantaneous rate) of some event (known as hazard function for survival analysis) at any time t:

$$\lambda(t;\mathbf{w}) = \lambda_0(t)\ \exp\{\mathbf{w}'\boldsymbol{\theta}\} \qquad [1]$$

where $\lambda_0(t)$ is the baseline hazard function or average hazard (of, e.g., culling) at time t; and $\mathbf{w}$ is a vector of covariates. In the Cox model, $\lambda_0(t)$ is unspecified; $\mathbf{w}$ is a vector of continuous or binary indicator covariates such as disease, parity, and milk yield; and $\boldsymbol{\theta}$, also a vector, represents the corresponding regression coefficients.

Five models were developed to study the effect of disease on culling. Model 1 (Equation [2]) treats disease as a binary covariate: 0 indicates that the cow is free of disease over the entire lactation, and 1 indicates that the cow has a disease at some point during lactation:

$$\lambda(t;\mathbf{x},\mathbf{z}) = \lambda_0(t)\ \exp\{\mathbf{w}'\boldsymbol{\theta}\} = \lambda_0(t)\ \exp\{\mathbf{x}'\boldsymbol{\beta} + \mathbf{z}'\boldsymbol{\gamma}\}. \qquad [2]$$

Here, $\mathbf{w}$ is split into two parts: $\mathbf{x}$ is a vector of covariates other than disease, and $\mathbf{z}$ is a vector with two indicator variables, one for healthy status and one for disease occurrence. Also, $\boldsymbol{\theta}$ is split into two corresponding vectors, $\boldsymbol{\beta}$ and $\boldsymbol{\gamma}$ ($\boldsymbol{\gamma}' = \gamma_h\ \gamma_i$). The subscripts h and i refer to a healthy cow and an ill cow, respectively. For a healthy cow, if $\mathbf{z}' = (1\ 0)$, then $\lambda(t;\mathbf{x},\mathbf{z}) = \lambda_0(t)\exp\{\mathbf{x}'\boldsymbol{\beta} + \gamma_h\}$. For a cow with a disease, if $\mathbf{z}' = (0\ 1)$, then $\lambda(t;\mathbf{x},\mathbf{z}) = \lambda_0(t)\exp\{\mathbf{x}'\boldsymbol{\beta}\}\exp\{\gamma_i\}$; that is, her hazard is multiplied by $\exp\{\gamma_i\}$. Because of estimability constraints, only the contrast of $\gamma_i - \gamma_h$ is estimable, and, without loss of generality, we can assume $\gamma_h = 0$, treating the healthy cow as the reference.

The primary problem with Model 1 is that it assumes that the effect of disease on culling is constant over the entire lactation, even before the cow develops the disease. It would be more realistic to assume that the hazard changes following diagnosis of the disease or the effect of the disease. Thus, in the next model, Model 2 (Equation [3]), the vector $\mathbf{z}$ is considered to be time-dependent:

$$\lambda(t;\mathbf{x},\mathbf{z}(t)) = \lambda_0(t) = \lambda_0(t)\ \exp\{\mathbf{x}'\boldsymbol{\beta} + \mathbf{z}'(t)\boldsymbol{\gamma}\} \qquad [3]$$

that is, $\lambda_h(t;\mathbf{x},\mathbf{z}'(t) = (1\ 0)) = \lambda_0(t)\exp\{\mathbf{x}'\boldsymbol{\beta} + \gamma_h\} = \lambda_0(t)\exp\{\mathbf{x}'\boldsymbol{\beta}\}$ while the cow remains healthy (assuming $\gamma_h = 0$ as before) and $\lambda_i(t;\mathbf{x},\mathbf{z}'(t) = (0\ 1)) = \lambda_0(t)\exp\{\mathbf{x}'\boldsymbol{\beta} + \gamma_i\}$ as soon as the cow becomes ill. With this model, the cow is considered to have a different hazard once she becomes ill: $\lambda_i(t) = \lambda_h(t)\exp\{\gamma_i\}$, where $\lambda_i(t)$ represents the hazard for a sick cow at time t, and $\lambda_h(t)$ represents the hazard for a healthy cow.

Model 3 helps determine whether the timing of the disease is important. Model 3 is the same as Model 2, except that $\mathbf{z}'(t)$ can take on different values, depending on when the disease occurs. For example, if four stages are defined in which disease can occur (1 to 60 d, 61 to 150 d, 151 to 270 d, and >270 d), then $\mathbf{z}'(t)$ can take on five values: one for healthy cows, one for disease occurring during the first 60 d, and one each for disease occurring between 61 and 150 d, 151 and 270 d, and after 270 d [i.e., (1 0 0 0 0), (0 1 0 0 0), ..., (0 0 0 0 1)]. Model 3 is an improvement over Model 2 because daily milk yield varies predictably with stage of lactation; the addition of the stage effect allows the actual events to be modeled more accurately.

Model 3 assumes that a cow has a different hazard, depending on the stage in which she becomes ill, but, after becoming ill, the cow has the same hazard on the day of occurrence, 1 wk later, and even 6 mo later. However, the effect of a disease is probably greatest immediately following disease, and the effect proba-

bly diminishes with time. It is reasonable to assume that an interaction may exist between time of disease occurrence and time of culling: the decision to cull may be made immediately (at time of disease), but the actual culling may not occur until much later in lactation. Model 4 incorporates the interaction between disease occurrence and stage of lactation (time of culling). Model 4 is the same as Model 2 or Model 3, except that $\mathbf{z}'(t)$ can take on different values depending both on when the disease occurred and when its effect on culling occurred.

For Models 1 to 4 (Cox models), the underlying distribution of survival times is unspecified. The baseline hazard function has been suggested to be closely approximated by a Weibull hazard function (5). Such an approximation greatly simplifies computations and provides baseline characteristics that can be summarized with only two parameters (ρ and λ). Model 5 is the Weibull counterpart to Model 4; the baseline is no longer unspecified but has a parametric form: $\lambda_0(t) = \lambda\rho(\lambda t)^{\rho-1}$, which is the Weibull hazard function.

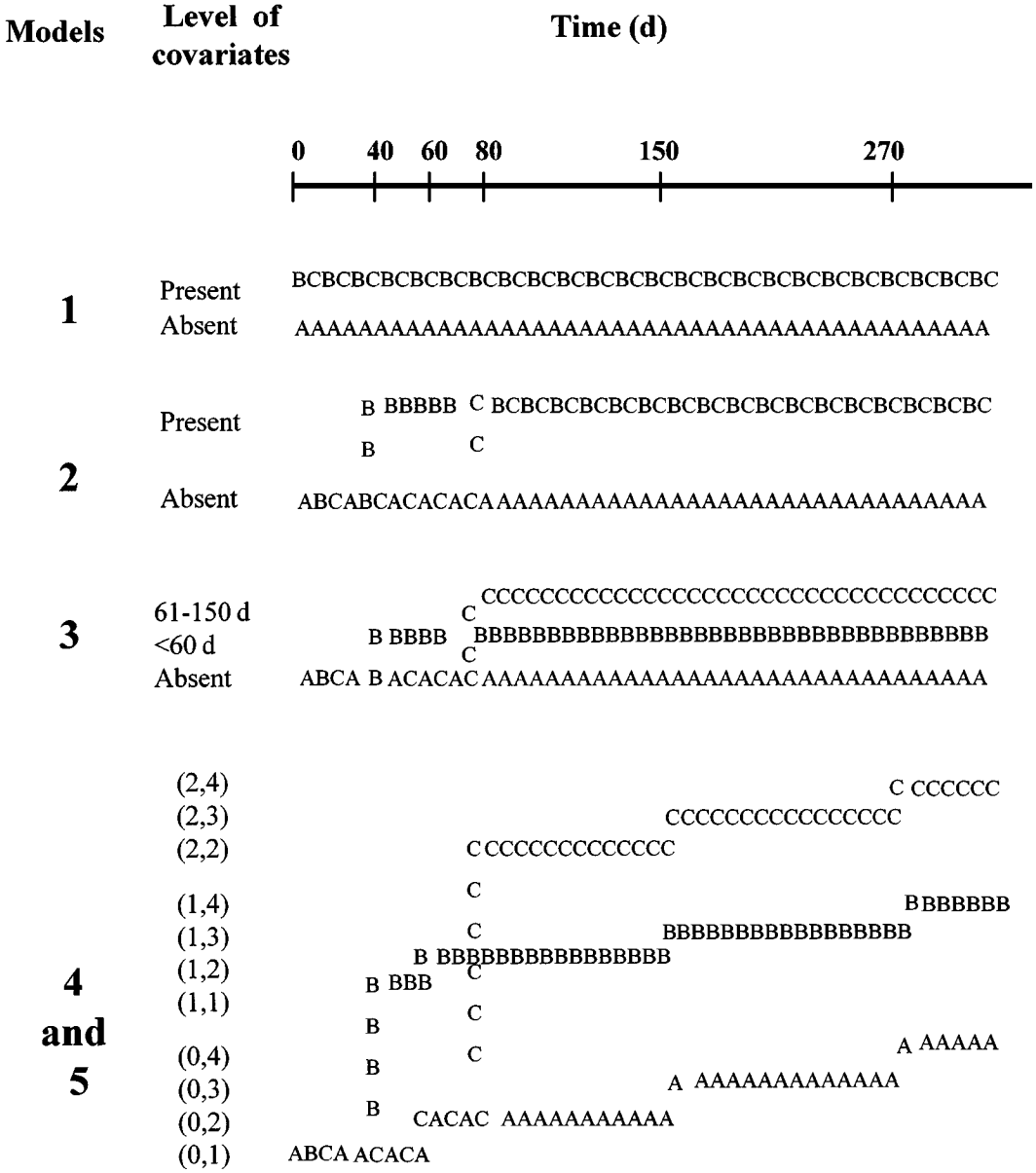

Figure 1. Illustration of the coding of the disease covariate for the various models, using three hypothetical cows: cow A, no mastitis; cow B, mastitis at 40 d; and cow C, mastitis at 80 d.

Figure 1 illustrates the coding of the categorical disease covariates for each of the models described. This coding does not pertain to the outcome (culling in this example). For each model depiction, the levels of the disease covariate are rising; these levels could just as easily be shown to be falling. What matters is that each level of the disease covariate is different from the previous level, not whether it is higher or lower. Three cows are shown: one remains healthy throughout lactation (cow A), one develops a disease at 40 d (cow B), and one develops a disease at 80 d (cow C). With Model 1, for each cow, the level of the disease covariate remains the same throughout lactation; the two sick cows are at a different level of the disease covariate than the healthy cow. With Model 2, for any sick cow, the level changes only at the time of disease, and the change is the same whenever disease occurs and thereafter. With Model 3, the level changes at the time of disease and is different depending on the stage of lactation in which the disease occurs; the level then remains the same thereafter. With Models 4 and 5, the level changes with the disease and the stage of lactation under consideration for both sick and healthy cows. Here (0, 1), (0, 2), (0, 3), and (0, 4) refer to the level of disease covariates for each stage of lactation for a healthy cow such as cow A. Because of overparameterization, the solutions for these levels [(0, 1) through (0, 4)] can be set to 0; (1, 1), (1, 2), (1, 3), and (1, 4) refer to the level of disease covariates during each stage of lactation (after onset of disease) for a cow developing disease before 60 d such as cow B, and (2, 2), (2, 3), and (2, 4) refer to the level of disease covariates during each stage of lactation (after developing disease) for a cow developing disease between 60 and 150 d such as cow C. The level of disease covariate is different for each stage of lactation, which illustrates the interaction between the time of disease occurrence and the time of culling.

Estimation Procedure

Parameters were estimated by maximum likelihood. A partial likelihood is actually used for the Cox models because they are semiparametric. The partial likelihood includes only the part of the full likelihood which does not depend on the unspecified baseline hazard function. All models were fitted using the The Survival Kit (6), a set of Fortran programs for Cox and Weibull models that allow for time-dependent and random variables.

Estimation of Hazards

When a model with time-dependent covariates is used, estimates of the parameters should be interpreted with great care. The knowledge of $\hat{\boldsymbol{\gamma}}$, a vector of estimated parameters, allows comparisons of the hazard at the same time point. But estimation of the hazard of animals at two different times involves the baseline hazard function, which also varies with time.

With Models 2 through 5, and assuming $\gamma_h = 0$ for a healthy cow,

$$\frac{\lambda_B(t)}{\lambda_A(t)} = \frac{\lambda_0(t)\exp\{x'\beta + \gamma_i\}}{\lambda_0(t)\exp\{x'\beta\}} = e^{\gamma_i} \quad [4]$$

for $t \geq 40$ and with the proper i in γ_i. Cow B is e^{γ_i} times more likely to be culled than is cow A at any $t \geq 40$. In particular, at occurrence of disease,

$$\frac{\lambda_B(40)}{\lambda_A(40)} = e^{\gamma_i}$$

and

$$\frac{\lambda_C(80)}{\lambda_A(80)} = e^{\gamma_j} \quad \text{(with the proper j)}.$$

Assume $\gamma_j > \gamma_i$. The previous results should not lead to the (possibly) erroneous conclusion that $\lambda_C(80) > \lambda_B(40)$ because what should be compared is $\lambda_B(40) = \lambda_0(40)\exp\{\mathbf{x}'\boldsymbol{\beta} + \gamma_i\}$ and $\lambda_C(80) = \lambda_0(80)\exp\{\mathbf{x}'\boldsymbol{\beta} + \gamma_j\}$ or, equivalently, $\lambda_0(40)\, e^{\gamma_i}$ and $\lambda_0(80)\, e^{\gamma_i}$, if $\mathbf{x}$ is independent of time.

Importantly, in order to adjust for changes in hazard throughout the lactation in a manner that is comparable with what is automatically done with the Cox model (by leaving the baseline completely unspecified), it is advisable to include in the Weibull model the time-dependent stage of lactation effects, η_i, as part of the vector of regression parameters $\boldsymbol{\beta}$. In such a case, $\mathbf{x}$ is dependent on time and $(40)^{\rho-1}\, e^{\eta_j + \gamma_i}$ and $(80)^{\rho-1}\, e^{\eta_j + \gamma_i}$ need to be compared, because, with the Weibull model,

$$\lambda_0(t) = \lambda_\rho(\lambda t)^{\rho-1} = \rho t^{\rho-1}\, e^{\rho \log\lambda}. \quad [5]$$

This comparison is more tedious with the Cox model, which requires $\hat{\lambda}_0(t)$ explicitly.

Predictions can be examined directly:

$$\hat{S}(t;\, \mathbf{x},\, \mathbf{z}) = \int_0^t \hat{\lambda}_0(u)\, \exp\{\mathbf{x}'\hat{\boldsymbol{\beta}} + \mathbf{z}'(u)\hat{\gamma}]du. \quad [6]$$

In other words, when $\hat{\boldsymbol{\beta}}$, $\hat{\gamma}$, and $\hat{\lambda}_0$ are known, $\hat{S}(t)$ can be obtained for any $\mathbf{x}$, $\mathbf{z}$, (or $\mathbf{z}(t)$) at any time t; survival curves can be predicted and used to compare the survival of groups of animals with different characteristics.

Likelihood Ratio Tests

How well the increasingly complex models fit the data can also be assessed by using likelihood ratio tests. The difference in the value of –2log(likelihood) between a reduced and a more complete model can be used to determine how well one model fits compared with another. The lower the value of –2log(likelihood), the better the model fits the data. The necessity of various terms in different models can be ascertained by comparing the difference in their –2log(likelihood) to the appropriate chi-square statistic; the correct degrees of freedom would be the difference in degrees of freedom between the two models. If the chi-square statistic is significant at the chosen α level, the extra term should remain in the model (9). This procedure can be performed repeatedly, for a sequence of nested models, such as Models 2 to 4.

An Example

The data. Data for 2998 Holstein cows of parity 2 and higher, and in 10 herds in New York State, were used to study the effect of mastitis on culling. Cows calved between January 1, 1994 and December 31, 1994 and were followed until September 30, 1995. The data were obtained from on-farm software marketed and supported by the Northeast DHIA. Data were collected on cow and herd identification, calving and culling (or censoring) dates, parity, previous 305-d milk yield, and date of occurrence, if any, of mastitis.

The models. The five models were fitted. The data were stratified by herd, which leads to the assumption of a different baseline hazard function, $\lambda_0(t)$, for each herd. In addition to a disease effect, all models contained class of previous 305-d milk yield (six classes) and parity. Previous 305-d milk yield was categorized into six levels within each herd and parity. Five of these represented different yield levels for cows of second or higher parity. The sixth level represented cows that did not have previous 305-d milk yield recorded. Parity had five levels, parities 2 through 5, and 6+.

For Models 3 and 4, the stage of lactation when the hazard is estimated (defined somewhat arbitrarily as ≤60 d, 61 to 150 d, 151 to 270 d, and >270 d) was not included as a covariate, but, for Model 5, it was. As already indicated, this difference is because the Cox proportional hazards model accounts for stage of lactation in the baseline hazard function, but the Weibull model does not, so, if stage were not included, cows without mastitis would not be adjusted for stage of lactation.

RESULTS AND DISCUSSION

Effect of Mastitis

The primary purpose of this study was to demonstrate the use of time-dependent covariates for survival analysis. In our demonstration, we used real data, with an applied question in mind: does mastitis occurrence increase the hazard of culling? The lactational incidence rate of mastitis in the 10 relatively large herds in this study was 18%. With all five models, older cows were more likely to be culled. As expected, higher previous 305-d milk yield was protective against culling. With all five models, mastitis significantly increased the hazard. Table 1 gives the hazard ratios for Models 4 and 5 (Cox and Weibull models, respectively), which included the interaction between mastitis and stage of lactation. In the column listing hazard ratios, each hazard is compared with a baseline hazard. The reference cow is healthy during parity 2, was in the lowest milk yield class during the previous lactation, and is considered during the first stage of her current lactation.

Table 2 lists culling hazard ratios from mastitis for each of the five models. Healthy cows were the reference. Model 1 treats mastitis as a time-independent covariate. A cow with mastitis was 1.3 times more likely to be culled than was a cow without mastitis; this hazard ratio applies to the entire lactation both before and after occurrence of mastitis. Model 2, in which mastitis is a time-dependent covariate that changes at time of disease, is more specific than Model 1. A cow with mastitis was 2.2 times more likely to be culled than was a cow without mastitis, at the time of occurrence and afterward, until the end of lactation. Model 3 assumes that the effect of mastitis on culling remains constant for a stage of lactation, but depends on when mastitis occurred (i.e., before 60 d, between 61 and 150 d, between 151 and 270 d, or after 270 d). These values divide the lactation curve into different parts. The different stages of lactation have different test day milk yields, which should affect the probability of being culled. The number and limits of these time intervals are somewhat arbitrary, and more research must be done to define them more objectively. With Model 3, the later in lactation that

mastitis occurred, the greater the hazard became, compared with that of a healthy cow; daily milk yield is also lower by this time. Model 3 is not as good as it could be because it is still not specific enough; the increase in the hazard from mastitis during each time period pertains to any time after mastitis. For example, if a cow had mastitis on d 65, the increase in the hazard of subsequent culling would be the same on d 66 as on d 270, according to Model 3. Inclusion of an interaction between mastitis and stage of lactation, as was done in Models 4 and 5, clearly shows the effect on culling at specific time periods because of mastitis, which itself occurs during specific time periods. The inclusion of the interaction is important because it reflects the actual situation better than do Models 1 through 3. The timing of mastitis has an effect on the time that subsequent culling occurs. If this effect were not the case, all of the estimates for the interaction would have been the same, and Model 3 would have been sufficient.

Figure 2 shows the estimated absolute hazard rates for each of Models 1 through 5. The hazard rate for the healthy cow is always lower than that of the sick cows. In Figure 2 (B through E), which accounts for the timing of disease in some way, the hazard rate for the healthy cow is the same as that for the sick cows until disease onset, when the hazard rate for the sick cows becomes higher. In Figure 2A, representing

TABLE 1. Hazard ratios and 95% confidence intervals (CI) for factors in Cox proportional hazards model and Weibull model (Models 4 and 5) with an interaction between occurrence of mastitis and stage of lactation for culling (2998 New York Holstein dairy cows calving in 1994).[1]

	Cox		Weibull	
Covariate	Hazard ratio	95% CI	Hazard ratio	95% CI
Parity				
2	1.0	...	1.0	...
3	1.6***	1.4, 1.9	1.6***	1.4, 1.9
4	1.9***	1.5, 2.3	1.9***	1.6, 2.3
5	2.6***	2.1, 3.3	2.6***	2.1, 3.3
6+	2.8***	2.2, 3.7	2.8***	2.2, 3.6
Previous 305-d milk yield				
1 (lowest)	1.0	...	1.0	...
2	0.9	0.7, 1.1	0.9	0.7, 1.1
3	0.7**	0.6, 0.9	0.8**	0.6, 0.9
4	0.7**	0.6, 0.9	0.7**	0.6, 0.9
5 (highest)	0.6***	0.5, 0.8	0.6***	0.5, 0.8
6[2]	1.2	0.7, 2.0	1.3	0.8, 2.1
Effect of mastitis during stage				
Baseline (no mastitis)	1.0	...	1.0	...
1, 1	2.4***	1.6, 3.5	2.2***	1.5, 3.2
1, 2	3.8***	2.5, 5.9	3.4***	2.3, 5.2
2, 2	6.0***	3.3, 10.9	5.3***	3.0, 9.4
1, 3	2.0***	1.4, 2.9	2.0***	1.4, 2.8
2, 3	2.3***	1.5, 3.6	2.2***	1.4, 3.5
3, 3	3.3***	2.0, 5.5	3.5***	2.2, 5.7
1, 4	1.3	0.9, 2.1	1.4	0.9, 2.2
2, 4	1.0	0.5, 1.9	1.1	0.6, 2.1
3, 4	1.6	0.9, 2.7	1.7	1.0, 2.8
4, 4	4.0***	2.1, 7.6	5.1***	2.8, 9.5
Stage of lactation				
1 (1 to 60 d after calving)	...	...	1.0	...
2 (61 to 150 d)	...	...	0.5***	0.3, 0.6
3 (151 to 270 d)	...	...	1.0	0.8, 1.4
4 (>270 d)	...	...	1.4	1.0, 1.9

[1]The effect of mastitis during a stage of lactation is denoted as follows: (stage 1, 1 to 60 d of lactation; stage 2, 61 to 150 d; stage 3, 151 to 270 d; and stage 4, >270 d): (i, j) = effect of mastitis occurring during stage of lactation i on culling observed during stage of lactation j. All effects are to be compared with the baseline condition of no mastitis.

[2]Cows in lactations 2 or greater are missing milk yield data.

*$P < 0.05$.

**$P < 0.01$.

***$P < 0.001$.

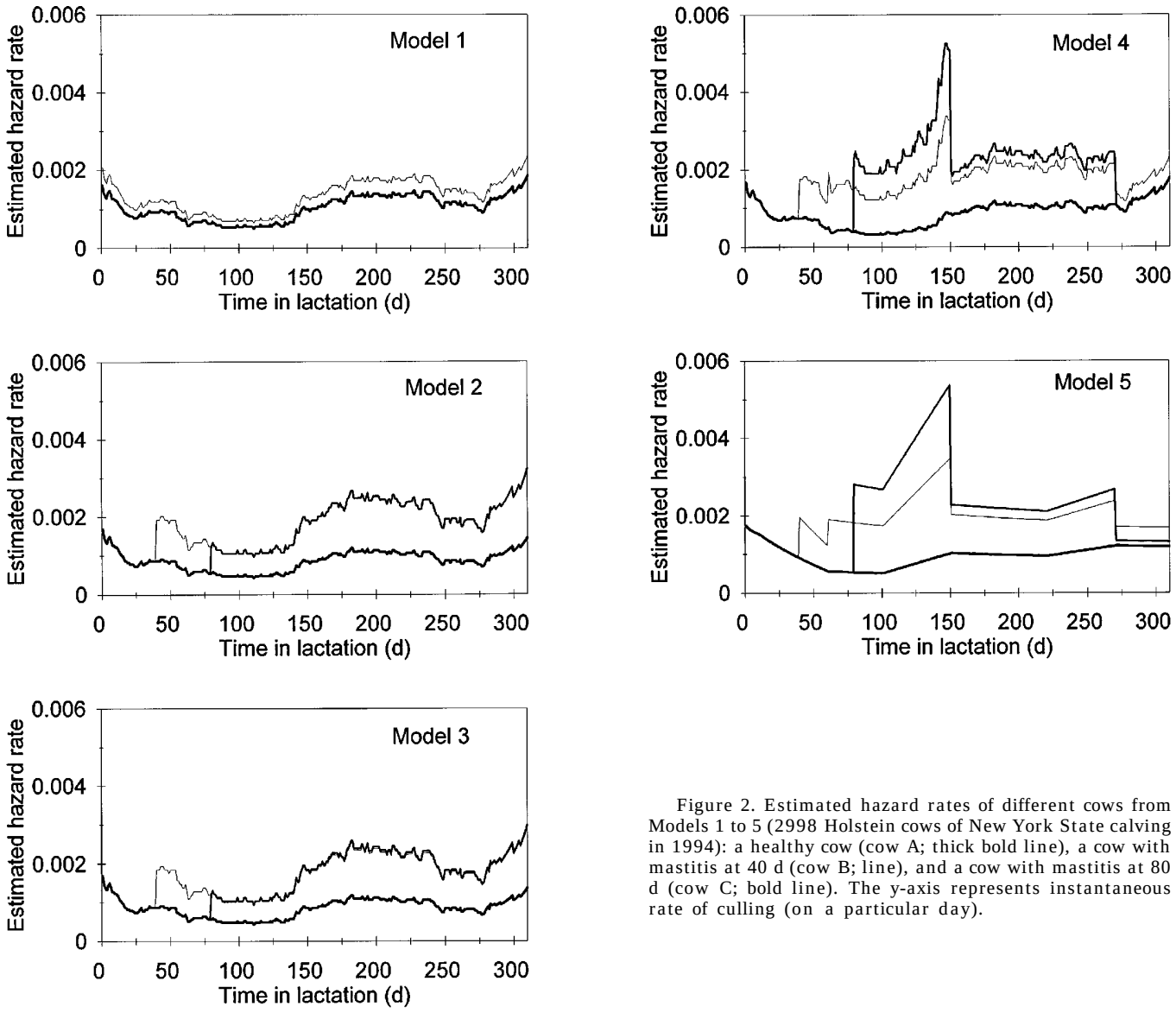

Figure 2. Estimated hazard rates of different cows from Models 1 to 5 (2998 Holstein cows of New York State calving in 1994): a healthy cow (cow A; thick bold line), a cow with mastitis at 40 d (cow B; line), and a cow with mastitis at 80 d (cow C; bold line). The y-axis represents instantaneous rate of culling (on a particular day).

Model 1, the estimated hazard rate of the two sick cows (which is the same for both) is higher than that of the healthy cow over the entire lactation. The two curves are proportional; the hazard of the sick cows is always 1.3 times (hazard ratio; see Table 2) greater than that of the healthy cow. In Figure 2B, representing Model 2, the estimated hazard rate for cow B is the same as that of the healthy cow (and of cow C) until d 40, when the cow contracts mastitis. Thereafter, the hazard rates for cows A and B are proportional. For cow C, the hazard rate is the same as that of the healthy cow until disease onset at d 80; thereafter, the hazard rates for cows B and C are identical because they are both multiplied by the same hazard ratio (2.2; see Table 2) after disease onset. In Figure 2C, representing Model 3, the hazard rate for cow C is only slightly higher than that of cow B (after 80 d) because the hazard ratio for mastitis for cow C is only slightly greater than that for cow B [2.2 vs. 2.1 (Table 2)]. In Figure 2D, representing Model 4, after 80 d, cow C had the highest hazard rate of all three cows during most of the rest of the lactation. After 270 d, however, the hazard for cows A and C were nearly identical, and the hazard of cow B was slightly higher. For cows B and C, the highest hazard of culling was between 110 and 150 d. In Figure 2E, representing Model 5, the overall shape of the hazard curves was similar to those of Figure 2D. The base-

line hazard rate (for the healthy cow) in Figure 2E was obtained directly from the estimates of Model 5. With the Cox model (Figures 2, A to D), the baseline hazard rate was computed by the survival kit (6). Figure 2E illustrates the advantage of a stage of lactation effect, which allows more flexibility in describing the trend of the true hazard.

The best way to compare culling hazards at different times is to combine the estimates of Table 2 with the estimates of the baseline hazard function and with other time-dependent effects such as stage of lactation. The ranking of the estimates is within stage of lactation. When hazard ratios for different stages are compared, the ranking may be different. For example, the estimate from Model 4 of (1, 1) (2.4) is larger than that of (1, 3) (2.0). This result may lead to the erroneous conclusion that the hazard is higher during the first stage of lactation than during the third stage. Such a relationship is true when a sick cow is compared with a healthy cow, but not when the true hazard value is compared because the baseline hazard is higher during the third stage for all cows (Figure 2D).

Both Cox and Weibull models were fitted in this study. Although the results from both models were similar, several differences should be pointed out. The Cox model contains both a nonparametric element and a parametric element. The former is the baseline hazard rate (λ_0), which is the same for all observations in a given stratum (i.e., rate is unspecified). The latter element is the vector of covariates, the parameters of which are estimated in the model. The effects of the covariates multiply the hazard by some factor. Because the underlying hazard is unspecified, the parameter estimates only describe the ratio of the hazard of 2 cows with and without that factor. The baseline hazard, $\lambda_0(t)$, is eliminated from the expression $\lambda(t; \mathbf{w}) = \lambda_0(t) \exp\{\mathbf{w}'\theta\}$ when the hazards of two subjects are compared at time t. This feature is an advantage as well as a disadvantage of the Cox model. This feature is advantageous because, without having to know the underlying distribution of event times, inference about parameter estimates is straightforward. The disadvantage of the canceling out of $\lambda_0(t)$ is that the absolute hazard of an event for a particular subject cannot be predicted directly (8) but can be predicted by estimating $\lambda_0(t)$, assuming θ is known and equal to its estimate.

The Cox model is, in a sense, much more flexible because no assumptions are necessary. However, the results, interpretation, and conclusions are very similar to those using the Weibull model, which offers other advantages [much simpler computations and baseline characteristics that can be summarized with only two parameters (ρ and λ)]. There were no significant differences in parameter estimates between the Cox and Weibull models (Table 1).

Another difference is that stage of lactation must be included explicitly as a covariate in the Weibull model, or estimates for healthy cows would not be adjusted for stage of lactation; estimates for mastitic

TABLE 2. Hazard ratios of culling because of mastitis in 2998 New York State Holstein cows calving in 1994.

	Model 1[1]	Model 2		Model 3		Model 4	Model 5
Absent	1.0	1.0		1.0		1.0	1.0
Present	1.3**	2.2***					
			<60 d	2.1***	1, 1	2.4***	2.2***
			61–150 d	2.2***	1, 2	3.8***	3.4***
			151–270 d	2.5***	2, 2	6.0***	5.3***
			>270 d	4.9***	1, 3	2.0***	2.0***
					2, 3	2.3***	2.2***
					3, 3	3.3***	3.5***
					1, 4	1.3	1.4
					2, 4	1.0	1.1
					3, 4	1.6	1.7
					4, 4	4.0***	5.1***

[1]Model 1, Cox model with binary, time-independent covariate for mastitis; model 2, Cox model with time-dependent covariate for mastitis, one change at time of occurrence; model 3, Cox model with time-dependent covariate for mastitis, changes at time of occurrence, 60 d, 150 d, 270 d; model 4, Cox model with time-dependent covariate for mastitis and interaction between occurrence of mastitis and stage of lactation; and model 5, Weibull model with time-dependent covariate for mastitis and interaction between occurrence of mastitis and stage of lactation.

*$P < 0.05$.

**$P < 0.01$.

***$P < 0.001$.

cows were already adjusted for stage because of the changes in culling hazard at the time of disease occurrence and at different stages of lactation. With the Cox model, this adjustment is already made, so stage of lactation need not be specified.

Predicted Values

The ability of the survival kit of Ducrocq and Sölkner (6) to compute predicted values can be used to study the survival curves of different hypothetical cows or models. For example, comparison of the survival curves of two cows of the same parity and milk yield but of different disease status might be desired.

Figure 3 shows the survival curves (i.e., the probability of survival) of the three hypothetical cows of Figure 1 (i.e., a healthy cow, a cow developing mastitis at 40 d, and a cow developing mastitis at 80 d, for each of the five models). All cows were assumed to have average milk yield (during the previous lactation) and to be in parity 2. At any time point, the survival curve shows what proportion of a certain group of cows (e.g., those that developed mastitis at 40 d) is still alive. The rate refers to the slope of the log(survival curve) for a certain group of cows (e.g.,

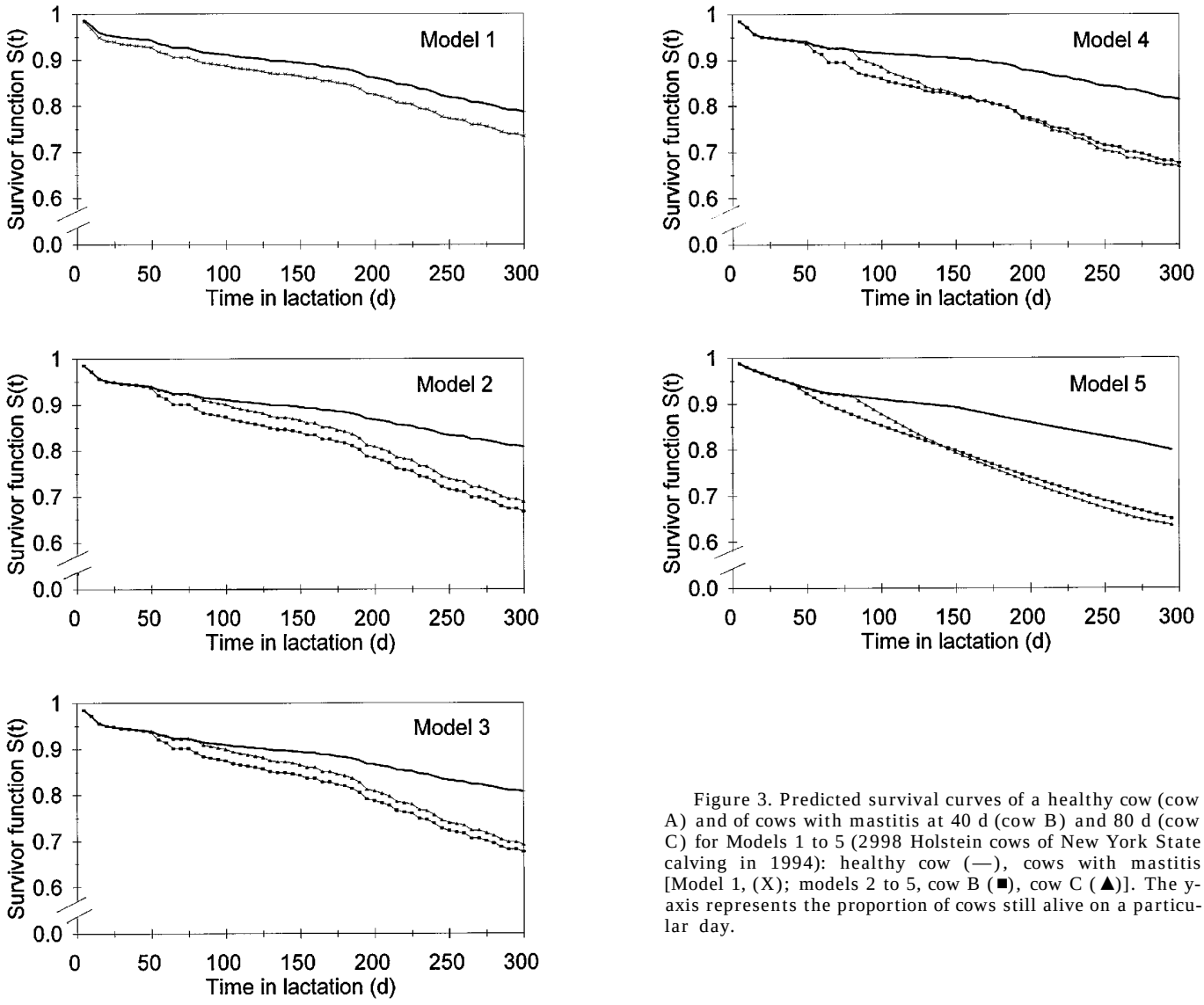

Figure 3. Predicted survival curves of a healthy cow (cow A) and of cows with mastitis at 40 d (cow B) and 80 d (cow C) for Models 1 to 5 (2998 Holstein cows of New York State calving in 1994): healthy cow (—), cows with mastitis [Model 1, (X); models 2 to 5, cow B (■), cow C (▲)]. The y-axis represents the proportion of cows still alive on a particular day.

those that developed mastitis at 40 d). Table 1 gives the hazard ratio for each group of cows compared with that of the reference group (defined earlier) during each time period or stage of lactation. The hazard ratios are directly associated with the rate of the survival curves. That is, by taking two time points, the rate of culling within that interval can be calculated. As the time interval shortens, the first derivative of the log(survival curve) with respect to time can be taken, and the instantaneous rate, or hazard, can be obtained.

The healthy cow, as expected, had the highest rate of survival over the lactation. When mastitis was accounted for, the survival rates were much lower. In Figure 3A, the survival curves for the two sick cows are identical because the model (Model 1) does not account for the timing of mastitis. Both cows are equally at risk throughout the entire lactation. In Figure 3B, the survival curves for the two sick cows are proportional after d 80 because the hazard for each of these cows is identical after the onset of mastitis (Model 2). In Figure 3C, the survival curves for the two sick cows are roughly proportional because their hazards are nearly identical (Model 3). In Model 4 (Table 1), between 61 and 150 d (stage 2), cows developing mastitis at 40 d (i.e., cow B) were 3.8 times more likely to be culled than were healthy cows (cow A). At the same stage (but only after 80 d), cows developing mastitis at 80 d (cow C) were 6.0 times more likely to be culled than were healthy cows. Although the survival curve for cow C would be expected to be lower than that of cow B, this relationship was not the case because the cows started out at different levels of culling, and some time was needed before the higher hazard (on a particular day) became evident (Figure 3D). In this particular case, the hazard for cows B and C overlaps between 150 and 200 d. After 200 d, cow C has a higher hazard (or lower survivor function). In Figure 3D, the slope of the curve for cow C is much greater than that for cow B between 80 and 100 d. The reason that the survival curve for cow C is higher than that for cow B is that a lag effect occurs, as has been explained. The rate of change over any time period is the measure that corresponds to the hazard ratios. The same explanation also applies to the shape of the survival curves of Figure 3E.

Likelihood Ratio Tests

The results suggest that the more complex the model is, the more realistic it is. A formal way to ascertain this relationship is to compare the models using likelihood ratio tests. Table 3 lists the –2log(likelihood) of each model and of a reduced model containing only parity and previous 305-d milk yield [i.e., occurrence of mastitis (Model 0) excluded]. Models 2 through 4 cannot be compared with Model 1 because the latter is not nested within any of the other models. The degrees of freedom associated with occurrence of mastitis are also given. Mastitis is highly significant for all models and increases as complexity increases. Consideration of an interaction between mastitis occurrence and stage of lactation was important, especially for the time of culling. Inclusion of the time of mastitis occurrence (Model 3) did not improve the fit of the model significantly (from Model 2; note the similarity between Figure 2, B and C, and between Figure 3, B and C), but consideration of the interaction between the time of

TABLE 3. Comparison of the model likelihoods (2998 New York State Holstein cows calving in 1994).

Model[1]	df[2]	–2 Log L[3]	Change in likelihood[3]	*P*	df	Change in likelihood[4]	*P*
0 (Cox)	0	9426.3	...	...	...	...	...
1 (Cox)	1	9417.4	8.9	<0.01	...	...	...
2 (Cox)	1	9345.7	80.6	<0.0001	...	...	...
3 (Cox)	4	9340.5	85.8	<0.0001	3	5.2	<0.20
4 (Cox)	10	9313.8	112.5	<0.0001	6	26.7	<0.0001
0 (Weibull)	0	13,772.2	...	...	...	...	...
5 (Weibull)	10	13,669.2	103.1	<0.0001	...	...	...

[1]0, Model contains parity and previous 305-d milk; 1, model 0 plus binary term for mastitis; 2, model 0 plus term for mastitis (one change at time of mastitis); 3, model 0 plus terms for mastitis (changes at time of mastitis; effect is different during different stages of lactation); 4, model 0 plus terms for mastitis (interaction between mastitis and stage of lactation); and 5, model 0 plus terms for mastitis (interaction between mastitis and stage of lactation).

[2]Degrees of freedom associated with mastitis.

[3]–2 Log likelihood; values have been compared with those of Model 0.

[4]Values have been compared with those of the model on the previous line.

mastitis occurrence and stage of lactation (Model 4) did significantly improve the fit of the model (from Model 3).

Possible Confounding

The purpose of epidemiological research is to obtain valid estimates through a properly designed study that controls possible confounding of factors during data analysis. In this study, parity and previous 305-d milk yield were included in all models as possible confounders. Older cows were more likely to be culled than were younger cows, and cows with higher milk yield were less likely to be culled than cows with lower milk yield. In this particular example, whether or not to include milk yield in the model and, if so, in which form, depended on the goal of the study. Five different strategies could be proposed: 1) no milk yield in the model, 2) inclusion of previous 305-d milk yield, 3) inclusion of cumulative milk yield of the first 60 d of the current lactation (or some other measure during early lactation, such as peak milk yield), 4) inclusion of a combination of the previous 305-d and first 60-d cumulative milk yield, and 5) inclusion of the current milk yield (e.g., in the form of the test day milk weights). Unfortunately, each of these strategies has certain drawbacks.

If the primary interest is to estimate the effect of disease on culling, rather than the indirect effect through milk yield (or any other covariate), including milk yield (an intervening variable) in the model (10) is wrong. However, the no milk yield option (strategy 1) may not properly address the possibility that a certain category of cows (e.g., cows with highest milk yield) is more susceptible to mastitis. The effect of mastitis may be underestimated if no adjustment is made for milk yield because these high yielding cows are much less likely to be voluntarily culled. Strategies 2 to 4 try to address this concern. Some difficulties may also arise from these approaches. By including cumulative 60-d milk yield of the current lactation (or peak milk yield) (strategy 3), some cows are excluded from the analysis because they have already been culled before a milk measurement is available. Exclusion of these cows introduces selection bias because the cows that are missing milk weights are very likely to be those that are culled during early lactation. An advantage of using the cumulative 60-d milk yield of the current lactation (or peak milk yield) is that dairy producers are more likely to make decisions based on milk yield during the current lactation than on milk yield during the previous lactation. Nevertheless, the selection bias is a major concern. Using the 305-d milk yield of the previous lactation (strategy 2) would avoid this problem but would exclude heifers. In our example, 305-d milk yield of the previous lactation was used, and a separate category was created for cows missing previous 305-d milk yield. In this way, all observations could be included for cows of parity 2 and higher, even those culled very early in the current lactation (e.g., before 60 d). Perhaps the most reasonable approach is to use the previous 305-d yield until peak milk yield (heifers would have their own category, unknown milk yield, because they have no previous milk yield), and, after the peak, the cumulative milk yield for the first 60 d could be used (strategy 4). Even with this approach, the 60-d cumulative milk yield for diseased cows may be decreased.

A separate question is whether dairy producers make decisions based on disease or only on current milk yield. One way to address this is to add current milk yields (in the form of test day milk weights) to the model as time-dependent covariates (strategy 5) to see how much disease effects change from the model without current milk yields.

This study used previous 305-d milk yield so that all cows could be included, whether or not they were culled, during the entire current lactation. Other strategies for including milk yield are also possible. We caution that during actual data analysis of disease effect on culling, careful thought should be given about whether or not to include milk yield in the model and, if so, in what form.

This study demonstrated the use of time-dependent covariates in models for culling hazard to account for the effect of disease and its occurrence on culling hazard at four stages of lactation: ≤60 d, 61 to 150 d, 151 to 270 d, and >270 d. These intervals were somewhat arbitrary and could vary. Short intervals would allow study of the almost instantaneous effect of disease on culling. Other areas to which this technique could be applied include the study of the time from disease onset to cure or the time from a new feeding regimen to changes in metabolism. Time-dependent covariates could also be used for repeated occurrences of a disease within a lactation or repeated occurrences during different lactations by coding the second (and subsequent) occurrences differently.

CONCLUSIONS

The inclusion of time-dependent covariates in a model helps to determine the effect of the covariate at different times during the study period. Modeling one

summary measure fails to consider what is happening during smaller time periods and could result in erroneous conclusions. Inclusion of an interaction between occurrence of mastitis and stage of lactation, both time-dependent covariates, in the models in this study proved to be highly beneficial. The effect of mastitis on culling could clearly be seen during each stage of lactation. A greater understanding of the effects of this disease on culling hazard was attained with each subsequent model fitted. We demonstrated, by using a more appropriate methodology, that the effect of mastitis on culling was probably underestimated (compare Figures 2A and 2E and the chi-square for Models 1 and 4 in Table 3) with more traditional approaches such as Models 1 and 2. Time-dependent covariates are recommended for use whenever appropriate.

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