Repeated Occurrence of Basal Cell Carcinoma of the Skin and Multifailure Survival Analysis: Follow-up Data from the Nambour Skin Cancer Prevention Trial

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The aim of this study was to apply multifailure survival methods to analyze time to multiple occurrences of basal cell carcinoma (BCC). Data from 4.5 years of follow-up in a randomized controlled trial, the Nambour Skin Cancer Prevention Trial (1992–1996), to evaluate skin cancer prevention were used to assess the influence of sunscreen application on the time to first BCC and the time to subsequent BCCs. Three different approaches of time to ordered multiple events were applied and compared: the Andersen-Gill, Wei-Lin-Weissfeld, and Prentice-Williams-Peterson models. Robust variance estimation approaches were used for all multifailure survival models. Sunscreen treatment was not associated with time to first occurrence of a BCC (hazard ratio = 1.04, 95% confidence interval: 0.79, 1.45). Time to subsequent BCC tumors using the Andersen-Gill model resulted in a lower estimated hazard among the daily sunscreen application group, although statistical significance was not reached (hazard ratio = 0.82, 95% confidence interval: 0.59, 1.15). Similarly, both the Wei-Lin-Weissfeld marginal-hazards and the Prentice-Williams-Peterson gap-time models revealed trends toward a lower risk of subsequent BCC tumors among the sunscreen intervention group. These results demonstrate the importance of conducting multiple-event analysis for recurring events, as risk factors for a single event may differ from those where repeated events are considered.

carcinoma, basal cell; epidemiologic methods; neoplasms, multiple primary; proportional hazards models; skin neoplasms; survival analysis

Abbreviation: BCC, basal cell carcinoma.

Longitudinal study designs are widely used in epidemiologic research, and a variety of longitudinal data analysis methods have evolved as a result. The simplest longitudinal study design has an outcome that can occur only once, for example, death or diagnosis of a specified cancer, and, typically, evaluates the association of the outcome with a number of prior exposures to risk factors. Survival analysis, in which time from exposure to outcome is analyzed, is considered a powerful and flexible approach to identifying such associations. However, in studies where the outcome of interest can occur multiple times in one individual, this approach precludes measurement of the exposure effect on repeated occurrences and is thus inefficient. A simple way of analyzing these multiple-events data is to use event rate models, such as the Poisson or negative binomial, which uses the total number of events per a fixed period of time but ignores the time between repeated occurrences. In addition, it is not possible to identify whether the effect of exposures changes the rate of occurrence across the time period.

Cox’s proportional hazards model (1) is the most commonly used model for clinical trial data and provides reliable estimates of survival times, as well as the relative risk associated with time-to-event occurrence. As a semi-parametric model, it does not have any constraints on...
distributional assumptions, which makes it more attractive than a fully parametric model. However, survival time in the standard Cox model terminates at an event and discards any information past that point. One solution is to use multiple failure times instead of only the first, but the event times within individuals are correlated. Hence, the assumption of independence is violated using the standard Cox regression model, and this introduces statistical complications. To avoid error resulting from analyzing correlated repeated events, the time to first event is still commonly used for events that occur repeatedly.

Multiple-event analytical techniques for survival data have been developed during the last few decades (2–7) but, as a result of their complex structure and computational requirements, they have not been commonly applied. However, advancement in statistical software in recent years has made these methods more accessible to researchers. Although still uncommon, use of these methods has increased in recent years, especially in the areas of clinical research (8–12). Therneau and Grambsch (13) described these models in detail with examples, and Kelly and Lim (12) have provided a very comprehensive explanation of the models’ application to multiple-failure data, along with the appropriate assumptions. In addition, major statistical software programs, such as SAS (SAS Institute, Inc., Cary, North Carolina), SUDAAN (Research Triangle Institute, Research Triangle Park, North Carolina), and STATA (StataCorp LP, College Station, Texas), have now made these models accessible.

An important example of a disease outcome that occurs repeatedly within susceptible individuals is keratinocytic skin cancer. Basal cell carcinoma (BCC) of the skin is by far the commonest cancer occurring among Caucasians. BCC rarely causes death, and new BCCs can develop repeatedly in the same individual. Although people with a diagnosis of BCC are known to have an increased risk of developing new BCCs (14, 15) and although the incidence rises with multiple previous BCCs (10), very few studies (9) have examined the nature of repeated occurrence of this disease. Furthermore, the effect of sunscreen intervention on repeated occurrence has not been studied. Our aim was to study the benefit of retaining multiple events of BCC in survival analysis to study the effect of a daily sunscreen intervention and to compare the results from this multiple-failure time analysis with those from a time-to-first-event analysis.

Previously published analyses of these data revealed no significant association between daily sunscreen use and incidence of BCC when Cox regression was used to analyze the time to first event (14). These results also included an examination of the rate of BCC tumor occurrence over the trial period. However, the repeated outcome was incorporated in such a way that any delay in the process of developing a subsequent tumor for those using daily sunscreen was not considered. Since the latent period of BCC is unknown but may be as long as 20 years, it could be difficult to observe the effect of an intervention during only 4 years of surveillance. Furthermore, analysis of only the time to first tumor may overlook critical effects of the intervention and their timing. Since people with prior BCC(s) are up to 70 percent more likely to develop a subsequent BCC within 3 years (15), the likelihood of an observable sunscreen effect on later tumors rather than early ones in an individual is very high. Moreover, we hoped to achieve more power to estimate a global effect of sunscreen using multiple-events data compared with that from a single event.

The aim of this paper was to apply existing multivariate survival time models to data from the Nambour Skin Cancer Prevention Trial. The Andersen-Gill (5), Prentice-Williams-Peterson (4), and Wei-Lin-Weissfeld (6) marginal failure models for the time to multiple-failure events were applied to the development of many BCCs over time in individuals. Data were collected over 4.5 years of prospective follow-up. Multiple-failure marginal survival models were used to examine the temporal effect of sunscreen treatment.

MATERIALS AND METHODS

Specific details of the Nambour Skin Cancer Prevention Trial (also known as the Nambour Trial) have been reported previously (16, 17). In brief, the Nambour Trial was a 2 × 2 factorial field trial to test the efficacy of daily sunscreen application and beta-carotene supplementation for the prevention of skin cancer over 4.5 years of follow-up. Participants were residents of Nambour, a subtropical town of around 8,000 people lying 100 km north of Queensland’s capital, Brisbane. Nambour has one of the highest reported incidence rates of skin cancer in Australia, with BCC tumor rates of 5,821 and 2,733 per 100,000 person-years at risk among males and females, respectively (18). In 1986, 3,000 residents of Nambour randomly selected from the electoral roll (enrolment is compulsory) were invited to participate in a skin cancer prevalence survey. In 1992, 1,621 of the 2,095 people who had taken part in this survey were randomly assigned to one of four groups: 1) beta-carotene tablets and sunscreen, 2) placebo tablets and sunscreen, 3) beta-carotene only, or 4) placebo only. Those not allocated to daily use of sunscreen were asked to continue their usual discretionary sunscreen use (use of a placebo sunscreen was considered to be unethical in the Queensland climate).

The intervention phase of this trial continued until late 1996, and only histologically confirmed BCCs diagnosed during the intervention period were included in this analysis. In 1992, 1994, and 1996, specialist dermatologists carried out full-body skin examinations of trial participants, and all skin cancers were recorded. Any tumors clinically diagnosed as keratinocytic skin cancers were biopsied, and a single histopathologist reviewed all specimens. Between these examinations, participants reported any skin lesions treated by their physicians, and medical and pathology records were reviewed to validate all such reports. Linkage with the databases of all local pathology companies ensured that no histologically diagnosed skin cancers were overlooked.

With regard to statistical methods, the analysis examined the association between the sunscreen intervention and subsequent diagnosis of histologically confirmed BCC during the trial period. Four different models were applied.
to the data. The simplest model was the Cox proportional hazard model, using the time to diagnosis of first BCC as an outcome. This was compared with three multifailure survival models, all of which are generalized forms of the Cox model. Since an individual can get more than one BCC tumor at one time, an “episode” of BCC occurrence was defined as the occurrence of one or more tumors in an individual at a single point in time. The time to a new tumor episode was used as the endpoint for the multiple-failure models. Thus, a person with one tumor at a point in time is considered the same as someone with more than one tumor at that point in time. In multiple-failure models, multiple observations per individual are used, depending on the number of events (episodes) they have had during the study period. Episodes of tumors beyond the third occurrence were not used, because of the small number of times this occurred and because including them made the model unstable.

The Andersen-Gill approach (5) models the repeated tumor episodes for each person as separate observations, with the risk set not constrained by the number of events occurring within an individual, and makes a strong assumption of independence among multiple observations per person over time. However, a robust sandwich covariance matrix structure for the intraindividual correlation is used to overcome this assumption (13). Survival time for the Andersen-Gill model is calculated as the time since the beginning of the trial to the first episode and the time between episodes thereafter. It uses a common baseline hazard function for all events and estimates a global parameter for the intervention. Proportional hazard assumption with robust variance estimation was tested using scaled Schoenfeld residuals against log of time.

In the Wei-Lin-Weiﬀeld model, repeated episodes are stratified according to their order of occurrence, and the marginal analysis of each repeated event is performed separately using a Cox proportional hazard model without imposing any dependence structure in the model. In this model, the time for each episode starts from the origin of the study, and individuals with fewer than the maximum number are considered censored for the additional outcomes. The Wei-Lin-Weiﬀeld model estimates both global and event-specific parameters for the intervention. The global parameter is estimated by assuming that the resulting vector of estimates across strata is asymptotically jointly normal with a combined variance as a covariance matrix. A robust sandwich covariance technique is used to incorporate the correlation within individuals, but the order of occurrences is ignored. An event-specific hazard is estimated by stratified analysis that allows a separate hazard for each event.

As in the Wei-Lin-Weiﬀeld model, the Prentice-Williams-Peterson model analyzes the ordered multiple events by stratification. However, the stratification is based on the prior number of episodes during the follow-up period. Unlike the Wei-Lin-Weiﬀeld model where all participants are at risk in each stratum, the Prentice-Williams-Peterson model is a conditional model in which risk sets for the kth stratum are constrained to the individuals who have had k − 1 events. According to this model, all participants are at risk for the first stratum, but only those with an event in the previous stratum are at risk for the successive one. There are two approaches to modeling survival time in the Prentice-Williams-Peterson model: 1) the Prentice-Williams-Peterson total time model, where the time for each episode starts at the beginning of the trial; and 2) the Prentice-Williams-Peterson gap-time model, where the time starts at the beginning of the trial for the first episode and is restarted from the last episode for each repeated event. As with the Wei-Lin-Weiﬀeld model, the Prentice-Williams-Peterson model allows for event-specific baseline hazard functions for different strata of events. In this paper, we have considered the Prentice-Williams-Peterson gap-time model and made comparisons with the Wei-Lin-Weiﬀeld model to see whether gap-time modeling or total-time modeling was sensitive to the effect of sunscreen on repeated BCC events.

The analyses presented here were performed using the PHREG procedure in SAS/STAT statistical software (19). The proportional hazard assumption test was done using the cox.zph command in R software (20).

RESULTS

During the 4.5-year period of follow-up, 259 individuals of the initial 1,621 withdrew prior to completion for various reasons (24 because of death). The details of withdrawals have been addressed and shown to be noninformative elsewhere (14). The distribution of some known risk factors for skin cancer was compared between participants who dropped out and those who did not, to test whether the loss to follow-up was informative. There was no difference between the two sets of participants on skin color (p = 0.83), propensity to burn (p = 0.17), and lifetime occupation (p = 0.83), suggesting that loss to follow-up was generally random. In addition, as all the analyses are based on survival time, the follow-up time for the censored observations was compared between the sunscreen-intervention and control groups to check for bias due to nonuniform censoring patterns. The log-rank test suggested no evidence of such a difference (p = 0.87).

Over the 4.5-year period between February 1992 and August 1996, 179 of the 1,621 trial participants had at least one BCC. In total, 370 histologic BCCs were reported; the total number of histologically diagnosed BCCs per person over the period ranged from none to 18, with approximately 6 percent having only one, 2 percent having two BCCs, 1 percent having three BCCs, and less than 0.5 percent having four or more BCCs. The number of BCC episodes (as defined previously) ranged from none to seven, with approximately 7 percent having only one episode and 4 percent having two or more episodes of tumors. Figure 1 presents the frequencies of total BCC tumors and the number of BCC episodes among individuals with histologically confirmed BCC during 1992–1996.

Among 179 participants who had at least one BCC, 91 were from the sunscreen intervention group, and 88 were from the nonintervention group, with observed mean survival times to first BCC of 52.9 months and 52.3 months.
respectively. The log-rank test for homogeneity in survival curves indicated no significant association between allocation to the intervention group and time to first BCC \((p = 0.83)\) (figure 2A).

Of 179 people with a first episode, 45 did not have follow-up information past their first BCC for various reasons, such as withdrawal, end of the trial, and so on. Of the remaining 134 people, 63 (47 percent) had a second episode of histologic BCC, with an average interval time of 28.5 months (standard error = 2.1 months) and a median of 25.3 months since the first episode. This second episode was slightly delayed in the sunscreen intervention group (mean = 30.8 months, median = 30.6 months) compared with the nonintervention group (mean = 25.7 months, median = 24.0 months; figure 2B; log-rank \(p = 0.18\)). Subsequently, 54 percent of the 50 participants with a second episode had a third episode, and again the time interval was greater for the intervention group (mean = 24.0 months, median = 26.7 months) compared with the nonintervention group (mean = 19.3 months, median = 19.2 months; figure 2C; log-rank \(p = 0.31\)). BCC episodes beyond the third order were not used, as only 12 events were recorded in total. The interval between successive occurrences of BCC events narrowed for higher order events for both groups, with the intervention group having 3- to 5-month wider intervals than the nonintervention group. However, the small number of consecutive repeated events resulted in a lack of power to detect differences.

The global hazard ratios, along with their standard errors (i.e., 95 percent confidence intervals), were compared for the various models (table 1). For the Andersen-Gill
TABLE 1. Hazard ratios obtained from the multiple-failure time models for the combined effect of sunscreen intervention on repeated occurrence of basal cell carcinoma among 1,621 participants, Nambour Skin Cancer Prevention Trial, 1992–1996

<table>
<thead>
<tr>
<th>Models</th>
<th>Crude hazard ratio</th>
<th>95% confidence interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to first episode</td>
<td>1.03</td>
<td>0.77, 1.38</td>
<td>0.83</td>
</tr>
<tr>
<td>Andersen-Gill model†</td>
<td>0.90</td>
<td>0.66, 1.23</td>
<td>0.49</td>
</tr>
<tr>
<td>Wei-Lin-Weissfeld model‡</td>
<td>0.89</td>
<td>0.65, 1.24</td>
<td>0.50</td>
</tr>
<tr>
<td>Prentice-Williams-Peterson model‡</td>
<td>0.91</td>
<td>0.72, 1.15</td>
<td>0.42</td>
</tr>
</tbody>
</table>


multifailure survival model, the hazard ratio associated with the sunscreen intervention was 0.90 (95 percent confidence interval: 0.66, 1.23), which was lower than that for the time-to-first-episode model (hazard ratio = 1.03, 95 percent confidence interval: 0.77, 1.38). However, the standard error increased because of the overdispersion introduced by the multiple observations per individual. The test using the scaled Schoenfeld residual showed no evidence of proportional hazard assumption violation (p = 0.18).

The estimates obtained from the common-effect Wei-Lin-Weissfeld and Prentice-Williams-Peterson models (table 1) were quite similar to those from the Andersen-Gill model, except that the standard error for the Prentice-Williams-Peterson model was approximately 25 percent less than the other two, leading to a narrower confidence interval for the hazard ratio. Therneau (21) advised that the stratified Andersen-Gill model would be more appropriate than unstratified models if events occur in a causal path and if each effect increases the risk of having another event. There is no clear evidence to suggest that developing a BCC per se causes a subsequent BCC tumor, apart from factors that put a person in a high-risk category for multiple BCC tumors. Despite this, standard errors were 25 percent smaller from the stratified Andersen-Gill model compared with the nonstratified model.

When separate-effect models for each episode stratum were applied, the Wei-Lin-Weissfeld model revealed a systematic decrease in hazard ratio with an increasing number of events among the sunscreen intervention group (table 2). With the Wei-Lin-Weissfeld model, there were 30 percent and 41 percent reduced hazards among the sunscreen intervention group, compared with the nonintervention group, for the second and third episodes, respectively, with no effect being observed for the first episode (table 2). Similarly, the Prentice-Williams-Peterson gap-time model revealed decreasing hazards among the sunscreen intervention group by 29 percent for the second episode and by 33 percent for the third episode.

When defining episodes of events, we pooled people who had only one tumor with those who had a cluster of tumors at a single time point in one group, assuming them all to be at similar risk for the next episode. As the average interval time between successive tumors decreased for the higher order tumors, this assumption may not be valid. In order to verify this, we counted the total number of tumors an individual had at each episode. There were 24 people in the first episode, seven in the second episode, and three in the third episode who had more than one BCC tumor at a single point in time. Excluding them from the analysis decreased the estimated overall hazard ratio for the first occurrence by about 4 percent for all of Andersen-Gill, Wei-Lin-Weissfeld, and Prentice-Williams-Peterson models, with small increases in the standard error for the Andersen-Gill and Wei-Lin-Weissfeld models but a much-inflated standard error for the Prentice-Williams-Peterson gap-time model. Similarly, the hazard ratios for the effect of the intervention on the second and third occurrences using the Wei-Lin-Weissfeld model were reduced further after excluding the cases with more than one tumor at a time. The hazard ratio dropped to 0.61 for the second occurrence and to 0.54 for the third occurrence with corresponding 8 percent and 10 percent increases in the standard errors. The results from the Prentice-Williams-Peterson model were influenced in the same way as the Wei-Lin-Weissfeld model, with a reduction in the hazard ratio by about 14 percent for the second and by 13 percent for the third occurrences. However, the standard error of the parameter estimate was inflated by about 38 percent.

Personal history of skin cancer was also available for participating up to approximately 6 years prior to the trial.

TABLE 2. Hazards ratios comparing sunscreen interventions with noninterventions on repeated occurrence of basal cell carcinoma using the Wei-Lin-Weissfeld and the Prentice-Williams-Peterson gap-time multiple failure survival models, stratified by event episodes among 1,621 participants, Nambour Skin Cancer Prevention Trial, 1992–1996

<table>
<thead>
<tr>
<th>Wei-Lin-Weissfeld marginal proportional hazard model*</th>
<th>Prentice-Williams-Peterson gap-time model†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard ratio</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>First occurrence</td>
<td>1.03</td>
</tr>
<tr>
<td>Second occurrence</td>
<td>0.70</td>
</tr>
<tr>
<td>Third occurrence</td>
<td>0.59</td>
</tr>
</tbody>
</table>

When the time to first BCC after intervention was compared between the 166 people with and the remainder without a histologically confirmed BCC prior to the trial, the group with a BCC history had eight times the risk of developing another BCC (hazard ratio = 8.6, 95 percent confidence interval: 6.3, 11.6). This is consistent with results reported by others (9, 22, 23). These 166 participants were uniformly distributed among the intervention and nonintervention groups, and they contributed more than 50 percent of the total BCC episodes. As subjects with a prior history of BCC may be systematically different from those without such history, we analyzed the 166 high-risk participants using both Wei-Lin-Weissfeld and Prentice-Williams-Peterson models. A consistent decreasing trend in risk, with hazard ratios of 0.83, 0.78, and 0.63, respectively, for the first, second, and third occurrences was observed for the sunscreen intervention; however, none of these trends was statistically significant.

**DISCUSSION**

In this paper, we compared various multiple-failure survival models with the traditional Cox proportional hazard model to examine repeated episodes of basal cell carcinoma. The data were obtained from a clinical trial where participants were randomized in a $2 \times 2$ factorial design to daily sunscreen, discretionary use of sunscreen, beta-carotene supplementation, and placebo groups. The effect of daily sunscreen use, compared with discretionary sunscreen use, on the time to first event of BCC and the time to multiple events of BCC was analyzed and compared. Factors such as age, gender, and other potential confounders were evenly distributed among the groups (14) and, hence, not adjusted for in the analysis. We applied three different models for multiple-failure time and estimated both common/global effects and event-specific effects of the sunscreen intervention. All three common-effect models appeared to indicate that the daily use of sunscreen prolonged the time to repeated occurrence of BCC; however, the effects were not statistically significant. In addition, estimates of the global intervention effect were quite similar using all three models (Andersen-Gill, Wei-Lin-Weissfeld, and Prentice-Williams-Peterson gap-time models), with the robust standard errors slightly inflated for the Wei-Lin-Weissfeld model compared with the Andersen-Gill model, but the Prentice-Williams-Peterson gap-time model had about a 25 percent smaller standard error. The event-specific models, using the Wei-Lin-Weissfeld and Prentice-Williams-Peterson gap-time models, suggested a greater effect for repeated events than for the first one, with the hazard ratios consistently decreasing for later events. With the event-specific analysis, as has been previously reported (12), the Wei-Lin-Weissfeld model overestimated the effect of the sunscreen intervention for the second and third events, and the difference in the estimate was larger for the third than for the second event, using the Wei-Lin-Weissfeld model than the Prentice-Williams-Peterson model, with the robust standard error being similar in both.

We assumed there was within-subject correlation between BCC events. As simulations done by Kelly and Lim (12) showed that estimates of treatment effects decrease with increasing within-subject correlation, we explored further whether the true estimate of sunscreen intervention would have been greater with reduced correlation. Correspondingly, we excluded individuals presenting with multiple BCC tumors at one time point who might have contributed highly to the within-subject correlation. Applying the two event-specific models to the reduced data increased the estimates of the sunscreen intervention effect, suggesting that the true effect might have been influenced by a small number of individuals more susceptible to BCC tumors. The lower hazard associated with sunscreen found after excluding these high-risk cases suggests that some of the variability in the estimate of the effect may have been due to these cases who perhaps have a different pathway of BCC formation. These susceptible people may not gain as much protection from sunscreen as the normal population does. Although we did not see a significant statistical difference in time to first BCC episodes among daily sunscreen users compared with discretionary users, the trends of decreasing hazard ratio for each repeated episode suggest that the protective effect is greater for repeated occurrences than for the first event. The estimated standard error increased as the order of episode events increased using both the Wei-Lin-Weissfeld and the Prentice-Williams-Peterson models, indicating a lack of power to show statistical significance even though the estimates of hazard ratios were nearly halved. The effect of sunscreen was also stronger among the group of people with BCC prior to intervention, which supports the conclusion that sunscreen has a greater effect on repeated occurrences of BCC tumors. This emphasizes the importance of analyzing multiple-events data compared with a single event in a situation where a minority of people are at high risk of multiple events and the majority have none or one event.

As in all observational studies, there were limitations in the way our data were collected. Participants attended skin examinations at fixed time points, and many tumors not on easily visible sites were detected at these times. As a result, we had individuals with batches of tumors diagnosed at survey times and fewer tumors between the surveys (18). Recording the exact time of occurrence was difficult, as their existence may not be known until a full skin examination was performed. However, there is no reason to believe that this would have occurred differentially between the intervention and nonintervention groups, as the skin examination of almost equal proportions from each randomized group balanced the detection of events. By examining the cumulative hazard plot for detection of tumors (figure 3), one can see that, although major jumps occurred at each of the two survey periods (30 months and 58 months), the jumps were uniform in both the sunscreen intervention and discretionary groups, suggesting that the effect of intervention should not be unduly biased by this.

In conclusion, the multiple-failure time models appeared to provide us with a better picture of the effect of daily sunscreen use on repeated occurrence of BCC than was shown using a time-to-first-event model. Nonetheless, the
correlation among the tumor occurrences within individuals resulted in inflated standard errors and, combined with the small number of events, the analysis lacked the power to provide a statistically significant result.

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