Occurrence of metachronous basal cell carcinomas: a prognostic model

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ABSTRACT

Background: A third of patients with a first basal cell carcinoma (BCC) will develop subsequent (metachronous) BCCs.

Objectives: To study the prognostic effect of the number of previous BCC diagnosis dates a patient has experienced to derive a prediction model to assess the risk of metachronous BCCs that may inform individualized decision making on surveillance.

Methods: We considered participants of north-western European ancestry from a prospective population-based cohort study (Rotterdam Study). After linkage with the Dutch Pathology Registry, 1077 patients with a first BCC were included. Candidate predictors for metachronous BCCs included patient, lifestyle and tumour characteristics. The prognostic model was developed with Fine and Gray regression analysis to account for competing risk of death. We used bootstrapping to correct for within-patient correlation and statistical optimism in predictive performance.

Results: Second to fifth BCCs occurred in 293, 122, 58 and 36 patients, with median follow-up times of 3.0, 2.1, 1.7 and 1.8 years after the previous BCC, respectively. The risk of a new BCC was higher for patients with more metachronous BCCs. Having more than one BCC at diagnosis was another strong predictor of metachronous BCCs. Discriminative ability of the model was reasonable with an optimism-corrected c-index of 0.70 at 3 years.

Conclusions: The number of previous BCC diagnosis dates was a strong prognostic factor and should be considered when predicting the risk of metachronous BCCs. When the number of previous BCC diagnosis dates is combined with other readily available characteristics into a prognostic model, patients at high risk of a new BCC can be identified.

INTRODUCTION

Basal cell carcinoma (BCC) places a large burden on healthcare systems, resulting from the high incidence of new tumours over time (metachronous BCCs), which need treatment and follow-up.[1–4] The incidence of BCC is increasing, which is reflected in the significant increase in disability-adjusted life years and costs in different countries in the last decades.[2,5,6] Patients tend to develop subsequent skin cancers of the same type, illustrating the concept of field cancerization.[4,7,8] Most metachronous BCCs occur within the first 3 years after diagnosis, but the risk remains elevated over time.[4,9,10] A meta-analysis selected nine studies and found a pooled mean 5-year cumulative risk of a metachronous BCC of 36%, which was comparable with the most recent observational study published.[3,4]

We recently developed a prognostic model to discriminate between patients with a low risk and a high risk of a second BCC. Having more than one BCC at initial diagnosis was the strongest risk factor, followed by age, superficial first BCC and male sex.[11] These predictors have been found associated with metachronous BCCs in other observational research.[4,7,10,12–14] Previous studies have typically focused on the first metachronous BCC, whereas patients frequently develop more metachronous BCCs.[4,10] A prognostic model for metachronous BCCs could identify high-risk patients who need active surveillance, improving secondary prevention.

The question arises of whether the predictors of a second BCC will be predictive for the risk of metachronous BCCs. At least the number of previous BCC diagnosis dates a patient has experienced might be an important addition to the prognostic model. The purpose of our study was to determine the frequency and timing of metachronous BCCs with cumulative incidence curves and to develop a prognostic model to predict the absolute risk of metachronous BCCs. We analysed a prospective population-based cohort (Rotterdam Study)including > 1000 patients with BCC. In the model development, we considered death as a competing risk and adjusted for the multiple events per patient. Reporting was according to the TRIPOD Statement.[15,16]

MATERIALS AND METHODS

Study population

The Rotterdam Study is a prospective population-based follow-up study in a well-defined district of Rotterdam in the Netherlands and comprises 14 926 participants aged 45 years or older.[17] The cohort started in July 1989 and predominantly consists of people of north-western European ancestry. All the participants were interviewed and examined at baseline and these examinations were repeated about every 4 years. The

Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study). All participants provided written informed consent to participate in the study and for us to obtain information from their treating physicians.

Case definition

Identification of BCC cases has been described previously.[11] In short, the Rotterdam Study participants were linked to the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA) to obtain their medical history of histopathologically confirmed BCCs until 1 January 2014. PALGA was founded in 1971 and achieved complete national coverage in 1991.[18] The pathology excerpts we received contained information on date of diagnosis, anatomical location, body side, type of procedure (biopsy or excision), radicality (whether or not the BCC was completely excised with no tumour cells in the studied transection margins according to the pathologist) and diagnosis [including subtype(s)]. We used this information to distinguish metachronous BCCs from recurrent BCCs (i.e., irradically treated). Furthermore, if a new BCC was diagnosed within 6 months of an earlier BCC, it was considered to be present at the previous diagnosis date. This rule was applied during the entire follow-up period.

Of the 14 926 Rotterdam Study participants, 298 did not sign informed consent for a linkage and could not be linked to PALGA. To maintain the prospective design, participants who had a BCC before Rotterdam Study entry were excluded from the analyses.

All included patients had a first BCC with a date of diagnosis that served as starting point of the follow-up. Participants were followed from this point forward until they died, or reached the end of the linkage period (31 December 2013). We considered a maximum of four metachronous BCCs per patient, to have strata with at least 50 patients at time of prediction. Mortality dates were obtained from the municipal registry. Figure 1 shows the data structure of the BCC patients.

Candidate predictors

The same candidate predictors were considered as in our prognostic model for a second BCC: age at BCC diagnosis, sex, pigment status, tendency to develop sunburn, history of outdoor work, sun-protective behaviour, BCC localization, superficial subtype and having more than one BCC at date of diagnosis.[11] We added one new categorical predictor: the number of previous BCC diagnosis dates (0, 1, 2 or 3). More specifically, this predictor represents the number of previous diagnosis dates on which one or more BCCs were diagnosed. Pigment status was a combination of eye colour and hair

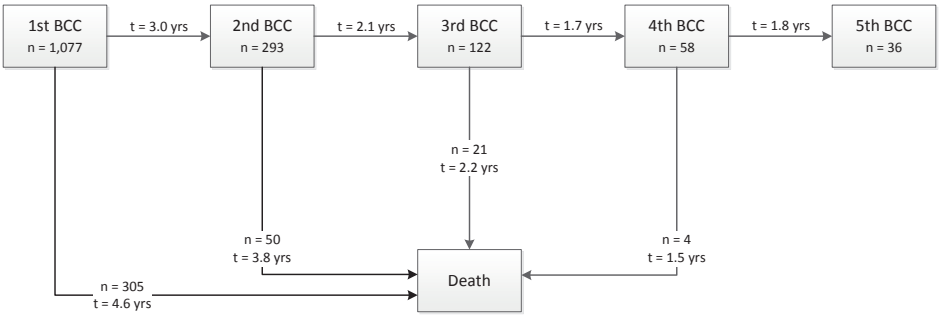

Figure 1. Structure of the metachronous basal cell carcinoma (BCC) dataset with numbers of patients (n) and median follow-up times in years (t)
Censoring occurred for 479, 121, 43 and 18 patients after having a first, second, third and fourth BCC diagnosis date, respectively.

colour when young. Mixed-type BCCs with a superficial component were coded as superficial. When participants had more than one BCC at a certain date of diagnosis, the localization and histopathological subtype at this date were randomly selected before the analyses. The latter was the case for 12– 25% of the patients, depending on the number of previous BCC diagnosis dates.

Model development

Missing predictor values were imputed 20 times using multivariate imputation by chained equations.[19] The imputation model included all candidate predictors, the outcome (i.e., new BCC, death or censored) and the follow-up time.

As a large proportion of the patients died during follow-up (24.5%), time to event analyses were adjusted for the competing event 'death'.[20] We used the Fine and Gray semiparametric proportional hazards model to estimate univariable and multivariable regression coefficients.[21] The subdistribution hazard of a new BCC corresponded to the absolute risk of a new BCC.

The proportionality of subdistribution hazards was tested for all predictors.[22] The assumption was not met for age, but adding an interaction term between age and time did not show sufficient relevance according to the likelihood ratio test to extend the model beyond the main effect of age. We explored the association of the continuous predictors with the risk of metachronous BCCs by plotting several transformations (linear, natural logarithm and square). Only the predictor age showed a nonlinear relationship with the outcome, which could be approximated by adding a quadratic term. To allow for event-specific effects of the predictors, we tested the interactions between the number of previous BCC diagnosis dates and each of the other predictors with likelihood ratio tests. None of these was of sufficient relevance to change the model specification.

The Fine and Gray model does not account for within-patient correlation resulting from multiple events per patient. Consequently, variance estimates of the regression coefficients will be too low and confidence intervals (CIs) will be too narrow. To adjust for the within-patient correlation, we assessed SEs with bootstrapping.[23] For each imputed dataset, we drew 1000 bootstrap samples. Backward stepwise selection was based on a liberal P-value (< 0.20), to reduce selection bias.[24] The regression coefficients in the final model were multiplied with a heuristic shrinkage factor.[25] Shrinkage was applied to prevent predictions for new patients being too extreme (i.e., low predictions being too low and high predictions being too high).

Model performance

We focused on discrimination as a key aspect of model performance. The discriminative ability of the model was evaluated using the concordance index (c-index) adapted for competing risks data.[26] In our survival data, the c-index represents the probability that, for a randomly chosen pair of patients, the patient who experiences a new BCC earlier in time has a higher predicted risk. A c-index of 0.5 is equivalent to a coin toss, whereas 1.0 implies perfect discrimination. We corrected the c-indices for optimism using a bootstrap procedure with 500 replications, including the backward selection procedure.[25]

Clinical application

We developed a score chart to facilitate clinical application of the final prognostic model. Scores were based on the shrunken regression coefficients, which were multiplied by 7.1 and then rounded to an integer. A constant was subtracted or added to rescale the scores conveniently. IBM SPSS Statistics for Windows version 21.0 (IBM, Armonk, NY, U.S.A.) was used for data management and R version 3.2.0 for more advanced statistical analysis,[27] using the 'cmprsk' and 'riskRegression' libraries.

RESULTS

Study population

After linkage, 1528 patients with at least one BCC were identified. Of those, 451 were excluded because they developed at least one BCC before entry into the Rotterdam Study. Included patients (n = 1077) had a median age of 75 years and 45% were male. Among them 293, 122, 58 and 36 developed a second, third, fourth and fifth BCC, respectively. The median follow-up until the next BCC was 3.0, 2.1, 1.7 and 1.8 years, respectively (Figure 1). In total, 380 patients died during a median follow-up for survivors of 5.0 years. The cumulative incidence of a metachronous BCC at 3 years

was 15%, 34%, 45% and 67% for the second, third, fourth and fifth BCC, respectively (Figure 2).

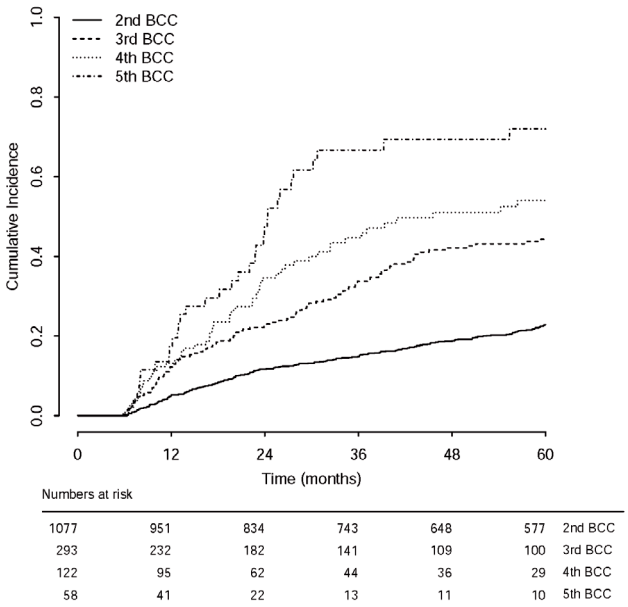

Figure 2. Cumulative incidence functions per basal cell carcinoma (BCC) diagnosis date sequence number
Below the figure are the number of patients at risk at the specific time points.

Predictors for metachronous basal cell carcinomas

The frequency of known predictors for a first BCC – such as light pigment status, easily sunburned and no sun protection-increased when patients experienced more metachronous BCCs (Table 1). More than one BCC at diagnosis was a strong predictor in the univariable analyses together with the number of previous BCC diagnosis dates a patient had experienced (Table 2). The effect of the localization of the BCC was similar for trunk and extremities.

Nine of the 14 candidate predictors remained in the multivariable model: age at BCC diagnosis, sex, pigment status, easily sunburned, coffee consumption, more than one BCC at diagnosis, superficial subtype of BCC, localization of BCC and the number of previous BCC diagnosis dates (Table 2). The apparent overall c-index of the multivariable model was 0.68 (95% CI 0.63–0.72) at 1 year; 0.71 (95% CI 0.69–0.74) at 3 years; and 0.69 (95% CI 0.67–0.72) at 5 years after any BCC diagnosis. Optimism-corrected c-indices were 0.67 (95% CI 0.62–0.71), 0.70 (95% CI 0.68–0.73) and 0.68 (95% CI 0.66–0.71), respectively.

Table 1. Distribution of candidate predictor values at first and metachronous basal cell carcinomas (BCCs)

		At 1st BCC N = 1077	At 2nd BCC N = 293	At 3rd BCC N = 122	At 4th BCC N = 58
Age at BCC diagnosis	Years	75 (68-81)	77 (71-83)	79 (73-84)	77 (73-85)
Gender	Male	484 (45%)	143 (49%)	68 (56%)	31 (53%)
Pigment status	Total[a]	928	255	105	52
	Dark	174 (19%)	42 (17%)	13 (13%)	6 (11%)
	Intermediate	514 (55%)	138 (54%)	56 (53%)	27 (52%)
	Light	240 (26%)	75 (29%)	36 (34%)	19 (37%)
Easily sunburned	Total[a]	1009	273	111	54
	Yes	365 (36%)	111 (41%)	55 (50%)	30 (56%)
Sun protection	Total[a]	1014	274	111	54
	Yes	404 (40%)	108 (39%)	35 (31%)	17 (31%)
Outdoor work	Total[a]	783	203	86	44
	Yes	142 (18%)	40 (20%)	19 (22%)	9 (20%)
BMI	Total[a]	1000	278	118	56
	Kg per m^2	26.0 (23.8-28.6)	25.9 (23.8-28.1)	25.8 (24.0-27.8)	26.6 (24.4-29.0)
Smoking	Total[a]	1059	284	117	56
	Ever	705 (67%)	188 (66%)	80 (68%)	36 (64%)
Alcohol consumption	Total[a]	836	241	101	48
	Glasses per week	3.8 (0.4-10.0)	3.5 (0.5-10.0)	4.0 (0.6-10.0)	2.5 (0.5-9.9)
Coffee consumption	Total[a]	836	241	101	48
	Cups per day	3.3 (2.0-5.0)	3.3 (2.0-4.0)	3.3 (2.0-4.0)	4.0 (2.9-4.0)
More than 1 BCC at diagnosis	Yes	132 (12%)	40 (14%)	30 (25%)	12 (21%)
Superficial BCC	Total[a]	1001	287	119	56
	Yes	199 (20%)	77 (27%)	37 (31%)	18 (32%)
Localization of BCC	Total[a]	1065	289	122	57
	Head	663 (62%)	165 (57%)	63 (52%)	25 (44%)
	Trunk	265 (25%)	84 (29%)	36 (29%)	24 (42%)
	Extremities	137 (13%)	40 (14%)	23 (19%)	8 (14%)

Data are n (%) unless otherwise indicated. IQR, interquartile range; BMI, body mass index. [a] For predictors with missing values, the number of observed values is given.

Table 2. Uni- and multivariable associations between predictors and occurrence of metachronous basal cell carcinomas (BCCs) using the Fine and Gray model for competing risks

Patient, lifestyle, and tumour characteristics	Coding	Univariable models HR (95% CI)[a]	Multivariable model HR (95% CI)[a]
Age at BCC diagnosis, years	69 versus 82[b]	1.3 (1.1-1.6)	1.4 (1.2-1.7)
Gender	Male	1.3 (1.0-1.6)	1.2 (1.0-1.4)
Pigment status	Dark	1.0	1.0
	Intermediate	1.3 (1.0-1.8)	1.2 (0.9-1.5)
	Light	1.6 (1.1-2.2)	1.3 (1.0-1.7)
Easily sunburned	Yes	1.4 (1.1-1.7)	1.2 (1.0-1.4)
Sun protection	Yes	0.8 (0.7-1.0)	—
Outdoor work	Yes	1.1 (0.9-1.4)	—
BMI, kg per m^2	24 versus 29[b]	1.0 (0.9-1.1)	—
Smoking	Ever	1.1 (0.8-1.3)	—
Alcohol consumption, glasses per week	10 versus 0[b]	1.1 (0.8-1.4)	—
Coffee consumption, cups per day	5 versus 2[b]	0.8 (0.7-0.9)	0.8 (0.7-0.9)
> 1 BCC at diagnosis	Yes	2.2 (1.8-2.6)	1.9 (1.5-2.4)
Superficial BCC	Yes	1.5 (1.3-1.9)	1.2 (0.9-1.5)
Localization of BCC	Head	1.0	1.0
	Trunk	1.5 (1.2-1.9)	1.2 (1.0-1.5)
	Extremities	1.4 (1.1-1.9)	1.3 (1.0-1.7)
Number of previous BCC diagnosis dates	0	1.0	1.0
	1	2.1 (1.7-2.6)	2.1 (1.7-2.6)
	2	2.8 (2.1-3.8)	2.6 (1.9-3.5)
	3	4.8 (3.4-6.9)	3.9 (2.5-6.2)

HR, hazard ratio; CI, confidence interval. [a] Based on 1000 bootstrap samples; [b] interquartile range.

Clinical application

A score chart was based on the regression coefficients of the final prognostic model (with shrinkage by a factor 0.89). The patient obtained a score for each predictor, and these were added to form a total score (Table 3). The corresponding predicted risks of a metachronous BCC are shown for 1, 3 and 5 years [Figure. 3; Table S1 (see Supporting Information)]. For example, a 75-year-old (4 points) male patient (1 point) with light pigment status (2 points), who sunburns easily (1 point), who drinks no coffee (4 points) and who presents for the first time (0 points) with one (0 points) superficial (1 point) BCC located at the head (0 points) has a total score of 13, which corresponds to a 3-year risk of 26% of experiencing a metachronous BCC. If this same male patient had presented with exactly the same BCC but already experienced three previous

BCCs, his score would be 22, corresponding to a 3-year risk of 59% of experiencing a metachronous BCC.

Table 3. Score chart for predicting metachronous basal cell carcinomas (BCCs)

Predictor	Value	Score
Age at BCC diagnosis, years	≤ 55	4
	60-70	5
	75	4
	80	3
	85	2
	≥ 90	0
Gender	Female	0
	Male	1
Pigment status	Dark	0
	Intermediate	1
	Light	2
Easily sunburned	No	0
	Yes	1
Daily intake of cups of coffee	0	4
	1-2	3
	3-4	2
	5-6	1
	≥ 7	0
More than 1 BCC at diagnosis	No	0
	Yes	4
Superficial BCC	No	0
	Yes	1
Localization of BCC	Head	0
	Trunk	1
	Extremities	2
Number of previous BCC diagnosis dates	0	0
	1	5
	2	6
	3	9
Total score		…

DISCUSSION

We studied the occurrence of metachronous BCCs and developed a prognostic model to predict the absolute risk of metachronous BCCs. The number of previous BCC

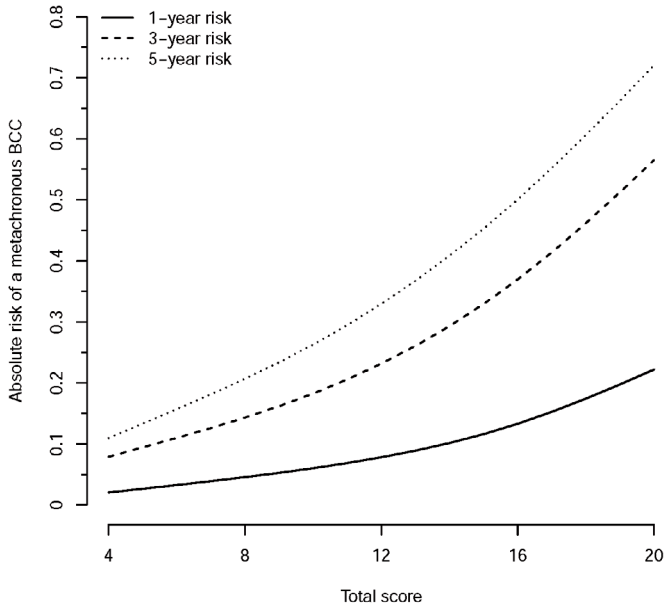

Figure 3. Total score obtained from the score chart (x-axis) and corresponding absolute risks of a metachronous basal cell carcinoma (BCC; y-axis) within 1, 3 and 5 years after the current BCC diagnosis date

diagnosis dates a patient experienced was the strongest prognostic factor. The risks of a third, fourth and fifth BCC increased compared with the risk of a second BCC. The number of previous BCC diagnosis dates was combined with easily obtainable patient, lifestyle and tumour-specific characteristics into a prognostic model.

Most predictors that were included in the current model and in our previous model for predicting a second BCC had similar effect sizes.[11] Three additional predictors with moderate effects were included in the model for metachronous BCC: pigment status, easily sunburned and localization of BCC.

The risk of a metachronous BCC was high in the first 2 years after a diagnosis, as illustrated by the cumulative incidence curves. Up to 50% of patients with a fourth BCC will develop a fifth within 24 months of follow-up. Indeed, previous studies have also shown that most metachronous BCCs occur within the first 2–3 years after diagnosis, but the risk remains elevated over time.[4,9,10] The model may guide in assessing individualized surveillance: who should be monitored and when, and extends our previous prognostic model, where we ended the follow-up after the first metachronous BCC (i.e., second BCC).[11]

Patients who experienced more previous BCCs were far more likely to develop a new BCC than patients who were diagnosed with their first BCC (Figure. 2). The number of previous BCC diagnosis dates and the number of BCC diagnosis dates at diagnosis

could be proxies of field cancerization, a well-known concept in patients with recurrent and multiple primary oral squamous cell cancers.[28] Like the oral cavity, the skin is one of the predominant sites of oncogenesis because it comes into direct contact with many carcinogens, in particular ultraviolet radiation (UVR). Throughout life, large fields of UVR-exposed skin accumulate genetically altered cells and become preneoplastic, which is analogous to, for example, head and neck squamous cell carcinoma of the digestive system.[29] Normal-looking human skin and epithelial tissue surrounding BCCs often contains precancerous changes, such as TP53 mutations.[30–32] Thus, physicians should always perform a full-body skin examination at first BCC diagnosis, because of the high likelihood of synchronous BCCs, and follow those who have a history of synchronous and/or metachronous BCCs. Our results are in line with other prospective U.S.-based follow-up studies, where the number of previous BCC diagnosis dates was the strongest predictor for metachronous BCCs in multivariable adjusted analyses.[7,33] A U.K. case–control study showed that the presence of more than one BCC at first presentation was significantly associated with a decreased time to the next BCC.[34]

Two other tumour-specific characteristics – histopathological subtype and localization – were also predictive of metachronous BCCs. The findings are comparable with U.K. case–control and cohort studies.[12,35] The results could indicate that patients with a superficial and/or BCC on the trunk or extremities comprise a subgroup in which different mechanisms are at work (e.g., different UVR exposure patterns and/or genetic susceptibility). However, in a Dutch retrospective cohort study both subtype and localization were not associated with a second BCC after multivariable adjustment.[36] Previous studies found that superficial BCCs are predominantly located on the trunk, whereas nodular BCCs are found more often in the head and neck area.[37–39] We noted a similar distribution of the different subtypes and localizations in our study.

The risk of metachronous BCCs increased with age but decreased again after approximately 68 years of age. This is similar to our previous finding, when we analysed the follow-up until the first metachronous BCC (i.e., second BCC).[11] Other prospective cohort studies have found a risk increase with age –but categorized age, which could have hidden a nonlinear relation.[7,10,13,33] Moreover, these studies also did not take the potential competing risk of death into account, which could lead to an unrealistic estimation of absolute risks.[20,40]

Our patients were relatively old (median age 75 years) as a result of linking the clinical data of the patients to the epidemiological data of the Rotterdam cohort containing mainly elderly people. Nevertheless, our model can be applied to patients from about 50 years of age, as the minimum age of our patients was 48 years.

Coffee consumption significantly reduced the risk of metachronous BCCs, for each increase of three cups of coffee per day the risk decreased by 20%. As discussed in our previous study, this could be a true biological effect or the result of selection

bias.[11] The findings on coffee consumption are diverse. A large prospective follow-up study from Australia showed protective effects of coffee consumption,[41] whereas two somewhat older European case–control studies did not find a significant association with BCC development.[42,43] A recent meta-analysis suggested a protective effect of coffee consumption, although this effect disappeared when the study that contributed the most heterogeneity between studies was left out of the analysis.[44] Despite these varying findings, the strong predictive effect of coffee consumption on developing a second or later BCC and the ease of asking patients about their coffee use allowed us to include this predictor in our model.

The apparent c-indices of our model varied between 0.68 and 0.71. As we had no external cohort, the c-index measured the internal validity of our model. But even after correcting for the possibly resulting optimism, the c-indices still varied between 0.67 and 0.70, which indicated a reasonable discriminative ability. As there are not yet any tools for predicting the occurrence of metachronous BCCs, we think our model is a good first step. We propose that the simple score chart can help physicians identify high-risk patients to prevent serious morbidity and high healthcare costs.[5,6] A cost-effectiveness analysis may identify a threshold value that justifies active surveillance and a reasonable frequency of follow-up.

The existing follow-up protocols differ per country and even per hospital within a country. Nevertheless, our model may well assist clinicians to better identify patients at high risk of metachronous BCC and to determine surveillance frequencies accordingly. For example, BCC patients in the Netherlands usually are not under follow-up, because 'only' 30% will get a next BCC and BCC is rarely lethal. Moreover, following up every patient would be unrealistic because of insufficient capacity and high costs. However, when clinicians can use our model to estimate an individual patient's absolute risk, they can decide to see high-risk patients regularly.

This study has some limitations. Some cohort members may have developed BCCs prior to the complete national coverage of PALGA; BCC diagnoses that were not based on pathology were missed (most likely only a small percentage);[45] and the UVR-related items in the questionnaires may not have been optimal. These issues were also encountered when we developed a model for a second BCC, but were shown to have little or no effect on the internal validity of the study design.[11] We did not have the availability of an external validation cohort and had to rely on bootstrap validation to support our claims of predictive performance in new patients. Future studies should validate the proposed score and try to improve the discriminative ability.[46]

To accommodate both competing risks and repeated events, we based our prognostic model on the Fine and Gray model. We corrected the variances of the predictor estimates post hoc to account for the within-patient correlation between metachronous BCCs. Other advanced techniques might have been used, such as the multistate model or the

joint frailty model.[47,48] Unfortunately, absolute risk calculation for repeated events is not yet readily possible with these techniques in currently available statistical software.

In conclusion, the absolute risk of a metachronous BCC can be predicted with reasonable accuracy using a prognostic model that consists of a combination of patient, lifestyle and tumour-specific characteristics. The number of previous BCC diagnosis dates a patient has experienced is the strongest prognostic factor with higher risk of a metachronous BCC, when patients have experienced more previous metachronous BCCs. When proven to be valid at external validation, the model can assist clinicians in identifying high-risk patients and in tailoring surveillance frequencies for individual patients.

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SUPPORTING INFORMATION

Table S1. Formula to calculate the individual absolute risks of metachronous basal cell carcinomas.

Table S1. Formula to calculate the individual absolute risks of metachronous BCCs

The predicted risk (%) of a new BCC within *t* years after the current BCC can be calculated as:

$$Pr = [1 - (\exp(-\exp(lp) \times CSH_0(t))] \times 100\%, \text{ where}$$

$$\begin{aligned} lp = {} & 0.145 \times (Age - 75) - 0.001 \times (Age^2 - 5746) + 0.141 \text{ (if male gender)} \\ & + 0.134 \times \text{(if intermediate pigment status)} \\ & + 0.221 \times \text{(if light pigment status)} \\ & + 0.166 \times \text{(if easily sunburned)} - 0.073 \times \text{(coffee cups per day} - 3.6) \\ & + 0.570 \times \text{(if more than one BCC}^a) + 0.146 \times \text{(if superficial subtype)} \\ & + 0.257 \times \text{(if localized on extremities)} \\ & + 0.166 \times \text{(if localized on trunk)} \\ & + 0.660 \times \text{(if 1 previous BCC diagnosis date)} + 0.849 \\ & \times \text{(if 2 previous BCC diagnosis dates)} + 1.220 \times \text{(if 3 previous BCC diagnosis dates)} \end{aligned}$$

$$CSH_0(1) = 0.033;\ CSH_0(3) = 0.109;\ CSH_0(5) = 0.163$$

[a] If more than 1 BCC is currently diagnosed, the observed value corresponding to the highest regression coefficient should be used for superficial and localization. BCC, basal cell carcinoma; $CSH_0(t)$, cumulative subdistribution baseline hazard at time point t in years; exp, exponent; lp, linear predictor; Pr, probability.