Predicting the risk of a second basal cell carcinoma

J.A.C. Verkouteren*
H. Smedinga*
E.W. Steyerberg
A. Hofman
T. Nijsten
* shared first authorship

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ABSTRACT

A third of basal cell carcinoma (BCC) patients will develop subsequent BCCs. We aimed to develop a simple model to predict the absolute risk of a second BCC. We observed 14,628 participants of Northern European ancestry from a prospective population-based cohort study. BCCs were identified using a linkage with the Dutch Pathology Registry (Pathological Anatomy National Automated Archive). Predictors for a second BCC included 13 phenotypic, lifestyle, and tumor-specific characteristics. The prediction model was based on the Fine and Gray regression model to account for the competing risk of death from other causes. Among 1,077 participants with at least one BCC, 293 developed a second BCC at a median of 3 years. Several well-known risk factors for a first BCC were not prognostic for a second BCC, whereas having more than one initial BCC was the strongest predictor. Discriminative ability at 3 years was reasonable (bootstrap validated c-index= 0.65). Three groups were created, with 7, 12, and 28% risk of a second BCC within 3 years. We conclude that a combination of readily available clinical characteristics can reasonably identify patients at high risk of a second BCC. External validation and extension with stronger predictors is desirable to further improve risk prediction.

INTRODUCTION

Patients with previously treated basal cell carcinoma (BCC) have a high risk of subsequent BCCs (Epstein, 1973). A recent meta-analysis showed that 29% of the patients with a first BCC will develop at least one more BCC (Flohil et al., 2013b). The increasing incidence of BCC, with ~ 5% annually, suggests that primary prevention campaigns have not been very effective so far (Lomas et al., 2012). Secondary prevention (i.e., detecting new BCCs at an early stage among patients with a prior BCC) is important to reduce the high disease burden (i.e., morbidity and costs) associated with this very common cancer (Housman et al., 2003; Flohil et al., 2013a; Hollestein et al., 2014).

The most well-known risk factor for a BCC is UVR, in particular acute and intermittent exposure (Kricker et al., 1995; Armstrong and Kricker, 2001). Recently, Weinstock coined the term "actinic neoplasia syndrome" to underline the fact that patients with a keratinocyte carcinoma (BCC or squamous cell carcinoma) frequently develop another keratinocyte carcinoma and various other signs of cutaneous photodamage (e.g., solar keratosis and actinic keratosis) due to the field dysplasia (Weinstock et al., 2009). However, BCC is a complex disease and not only UVR-related factors are important in its carcinogenesis.

In contrast to risk factors for a first BCC, prognostic factors for a second BCC are less well documented. Male sex, higher age at initial BCC, and a history of BCC have been found associated with metachronous BCCs (Karagas et al., 1992; Richmond-Sinclair et al., 2010; Flohil et al., 2011). The value of other phenotypic (e.g., skin type) and environmental (e.g., UVR) characteristics in predicting a new BCC is under debate (Robinson, 1987; Karagas et al., 1992; Lovatt et al., 2005; Kiiski et al., 2010; Richmond-Sinclair et al., 2010). However, no prediction models have been developed yet that allow for individualized risk stratification.

The objective of this study is to develop a prognostic model for predicting the occurrence of a second BCC. We hereto analyzed a prospective population-based cohort (Rotterdam Study; RS) including over a 1,000 BCC patients.

MATERIALS AND METHODS

Study population

The RS is a prospective population-based cohort study of people aged 45 years or older (Hofman et al., 2013). From July 1989 to September 1993, the first cohort of 7,983 recruited persons (RS-I, 78% of the invitees) aged 55 years or older was realized. In 2000– 2001, another 3,011 participants (RS-II, 67% of the invitees) who had become 55 years of age or older, or applied to this age minimum and had moved into the

district, were added to the cohort. The last addition of 3,932 Ommoord inhabitants (RS-III, 65% of the invitees) aged 45–54 years took place during 2006–2008. These three cohorts together comprise 14,926 participants. Data were acquired by interviews at home and by thorough examinations in a specially built research facility in their district. These examinations were repeated every 3–4 years. The RS 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: RS). All participants provided written informed consent to participate in the study and to obtain information from their treating physicians. The RS was conducted according to the Declaration of Helsinki Principles.

Case definition

The RS participants were linked to the Dutch nationwide network and registry of histopathology and cytopathology (PALGA) to retrieve their medical history of histopathologically confirmed BCCs. PALGA was founded in 1971 and achieved complete national coverage in 1991 (i.e., since 1991 all Dutch histopathology laboratories are linked to this databank; Casparie et al., 2007). Every pathology excerpt located on PALGA's central databank contains encrypted patient data and a PALGA diagnosis line derived from the Systematized Nomenclature of Medicine. In collaboration with a dermatopathologist, the following information from the excerpts was retrieved: date of diagnosis, anatomical location, body side, type of procedure (i.e., biopsy or excision), radicality, and diagnosis (including tumor subtype). To obtain all pathology reports concerning BCC, we used the PALGA diagnosis lines attached to all subtypes of BCC (i.e., M80903, M80913, M80923, M80933, M80943, M80963, M80973, and M80983).

The linkage was done using encrypted patient data both available in the RS and PALGA. This encrypted data consisted of the patient's date of birth, gender, and first four to eight letters of the (maiden) family name. The combination of these identifiers produced a linkage key. This key showed 98% sensitivity and 98% positive predictive value in earlier record linkage research (Van den Brandt et al., 1990).

Of the 14,926 RS participants, 298 did not sign informed consent for a linkage and could not be linked to PALGA. Every BCC excerpt between 1 July 1989 and 31 December 2013 was retrieved from the network of PALGA. Participants who had developed a BCC before entering the RS were excluded from the analyses.

All excerpts mentioned a date of diagnosis, and, the majority of excerpts included a precise anatomical location and information about the type of procedure and the radicality of the excision, which made it possible to distinguish between different BCCs over time. If information about location was not available, we assumed that a biopsy

followed by an excision within a logical time frame (<3 months) concerned the same BCC.

The next tumor following a radical excision was always scored as a new BCC. If an excision was irradical, the next reported tumor on the same or adjacent location was regarded as the same tumor. Metachronous BCCs occurring within 6 months of the first BCC were counted as additional tumors at the date of the initial diagnosis, as those BCCs were most likely present at this earlier date. If a BCC consisted of different histopathological subtypes, a superiority rule was used, namely infiltrative greater than micronodular greater than nodular greater than superficial. Unclear excerpts were discussed with an experienced dermatologist, and, if available, missing information was obtained from medical records.

Candidate predictors

Three phenotypic factors were selected—namely, age at first BCC (years), sex, and pigment status (Robinson, 1987; Karagas et al., 1992). The latter was a combination of eye color and hair color when young (e.g., a participant with blue eyes and red hair was scored as light). Hair color for RS-III was determined during the second examination round.

Three questions related to UVR exposure were selected and concerned the tendency to develop sunburn, a history of outdoor work for at least 4 hours per day during at least 25 years, and sun protective behavior measured by wearing sunglasses or a hat (Karagas et al., 1992). A history of outdoor work was not included in the questionnaire for the RS-II cohort. All UVR-related questions for RS-III were determined during the second examination round. In addition, smoking, alcohol consumption (glasses per week), coffee consumption (cups per day), and BMI (kg/m^2) were selected as other lifestyle factors (Freedman et al., 2003; Gerstenblith et al., 2012; Miura et al., 2014). Alcohol and coffee consumption for RS-II were determined during the third examination round.

Finally, three variables concerning BCC characteristics were included: localization of the first BCC, superficial histopathological subtype of the first BCC, and the number of BCCs at first date of diagnosis (Karagas et al., 1992; Lovatt et al., 2005).

Model development

All included participants had at least a first BCC and therefore have a date of first BCC diagnosis that served as starting point of the follow-up. Participants were followed from this point forward until they developed a second BCC, died, or reached the end of the linkage period (31 December 2013) without developing a subsequent BCC. Mortality dates were obtained from the municipal register. The localization and histopathological subtype of the first BCC of participants who had more than one BCC at the first date of diagnosis were randomly selected before the analyses.

Missing predictor values were imputed 50 times using multivariate imputation by chained equations (Van Buuren, 2012). The imputation model included all candidate predictors, the outcome (i.e., second BCC or censored), the follow-up time, the side of the first BCC, the level of education, and the RS cohort number.

As a large proportion (28%) of the elderly participants with a first BCC died before they could have developed a second BCC, the analyses were adjusted for competing risk of death from other causes (Wolbers et al., 2009). We used the Fine and Gray semiparametric proportional hazards model to estimate univariable and multivariable regression coefficients (Fine and Gray, 1999). The subdistribution hazard of the event of interest (i.e., second BCC) is the absolute risk of a second BCC. We explored the association of the continuous predictors with the risk of metachronous BCCs by plotting several transformations (e.g., linear, natural logarithm, or square).

We entered all (possibly transformed) candidate predictors in a multivariable model, independent of their p-values in the univariable models. To reduce the multivariable model with backward stepwise selection, we used Wald tests based on Rubin's rules for combining estimated regression coefficients and variances from the 50 different completed data sets (Vergouwe et al., 2010). To reduce selection bias, we used a liberal P-valueo0.20 to include predictors (Steyerberg et al., 2000; Steyerberg, 2009). No significant interactions were observed among the included predictors. The regression coefficients in the final model were multiplied with a shrinkage factor, which was estimated with bootstrapping (Steyerberg, 2009). Shrinkage was applied to prevent that predictions for new patients were too extreme (i.e., low predictions being too low and high predictions being too high).

We performed a sensitivity analysis by including only participants with complete data in the multivariable modeling.

Model performance

We focused on discrimination as a key aspect of model performance. The discriminative ability of the model was evaluated using the c-index. In the available survival data, the c-index represents the probability that, for a randomly chosen pair of patients, the patient who experiences a second 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 predictability. We corrected the c-indices for optimism using a bootstrap procedure (500 replications; Steyerberg, 2009).

Clinical application

For illustrative purposes, we divided patients in three risk groups (low, intermediate, and high) using the 25th and 75th percentiles of the risk score distribution as cut points. Next, a score chart was developed to facilitate clinical application of the final

prediction model. Scores were based on the shrunken regression coefficients, which were multiplied by 6.7 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 (Chicago, IL) was used for data management and R version 3.1.1 for more advanced statistical analysis (R Core Team, 2013), using the cmprsk and riskRegression libraries.

RESULTS

Study population

After the linkage between Pathological Anatomy National Automated Archive (PALGA) and the RS, 1,528 patients with at least one BCC were identified. Of those, 451 were excluded because they developed at least one BCC before entry of the RS. Overall, 1,077 patients were included, of whom 293 developed a second BCC during a median follow-up of 3.0 years, 479 did not develop a new BCC before the end of follow-up (median 3.8 years), and 305 died before they reached the end of follow-up (median 4.6 years; Table 1). The median age at first BCC in the overall group was 74.5 years, whereas in the group of participants who died it was 80.0 years. In all groups, there were more females than males.

Age at first BCC diagnosis

When using ordinary Cox models, there appeared a nonlinear relationship between age at first BCC diagnosis and the hazard of developing a second BCC (Figure 1a) and a linear relationship between age and the hazard of dying (Figure 1b). The subdistribution hazard of a second BCC—using the Fine and Gray model—also had a nonlinear relationship with age (Figure 1c). Compared with the cause-specific hazard, the subdistribution hazard of developing a second BCC is lower for older age, because it takes into account the fact that people may die and therefore are no longer at risk of a second BCC. The nonlinear relation between age at first BCC diagnosis and developing a second BCC could best be approximated by adding a squared term for age to the model.

Predictors for a second BCC

Of the 13 potential predictors, a lower age at first BCC (hazard ratio (HR): 1.6, 95% confidence interval (CI): 1.3–2.0 for 13 years younger) and two tumor-specific factors (i.e., superficial subtype of the first BCC and more than one BCC at first date of diagnosis) were significantly associated with an increased risk of a second BCC in the univariable analyses (Table 2). Furthermore, several other characteristics showed

Table 1. Characteristics of 1,077 patients from the Rotterdam study with at least a first BCC diagnosis

Patient and tumor characteristics	Category	Overall	New BCC	Death without new BCC	Alive without new BCC
Number of patients		1,077 (100%)	293 (100%)	305 (100%)	479 (100%)
Follow-up time (years)	Median (IQR)	3.8 (1.7-7.2)	3.0 (1.3-5.6)	4.6 (2.0-7.7)	3.8 (1.8-7.3)
Age at first BCC (years)	Median (IQR)	74.5 (67.6-80.7)	73.1 (67.3-77.6)	80.0 (74.6-85.6)	71.8 (65.4-78.7)
Sex	Male	484 (45%)	143 (49%)	137 (45%)	204 (43%)
BMI (kg/m^2)	Median (IQR)	26.0 (23.8-28.6)	25.9 (23.8-28.1)	26.5 (24.3-29.0)	25.9 (23.7-28.4)
	Missing	77 (7%)	15 (5%)	33 (11%)	29 (6%)
Pigment status	Dark	174 (16%)	42 (14%)	41 (13%)	91 (19%)
	Intermediate	514 (48%)	138 (47%)	135 (44%)	241 (50%)
	Light	240 (22%)	75 (26%)	74 (24%)	91 (19%)
	Missing	149 (14%)	38 (13%)	55 (18%)	56 (12%)
Easily sunburned	Yes	365 (34%)	111 (38%)	92 (30%)	162 (34%)
	Missing	68 (6%)	20 (7%)	20 (7%)	28 (6%)
Outdoor work	Yes	142 (13%)	40 (14%)	50 (16%)	52 (11%)
	Missing	294 (27%)	90 (31%)	43 (14%)	161 (34%)
Sun protection	No or almost never	404 (38%)	108 (37%)	133 (44%)	163 (34%)
	Missing	63 (6%)	19 (6%)	19 (6%)	25 (5%)
Smoking	Current or ever	705 (65%)	188 (64%)	198 (65%)	319 (67%)
	Missing	18 (2%)	9 (3%)	3 (1%)	6 (1%)
Alcohol consumption (glasses/week)	Median (IQR)	3.8 (0.4-11.2)	3.5 (0.5-11.2)	3.1 (0.2-11.1)	4.3 (0.3-11.2)
	Missing	241 (22%)	52 (18%)	86 (28%)	103 (22%)
Coffee consumption (cups/day)	Median (IQR)	3.3 (2.0-5.0)	3.3 (2.0-4.0)	4.0 (3.0-5.0)	3.3 (2.0-5.0)
	Missing	241 (22%)	52 (18%)	86 (28%)	103 (22%)
Localization of first BCC	Head	663 (62%)	175 (60%)	207 (68%)	281 (59%)
	Extremities	137 (13%)	35 (12%)	32 (10%)	70 (15%)
	Trunk	265 (25%)	81 (28%)	59 (19%)	125 (26%)
	Missing	12 (1%)	2 (1%)	7 (2%)	3 (1%)
Superficial first BCC	Yes	199 (18%)	64 (22%)	39 (13%)	96 (20%)
	Missing	76 (7%)	22 (8%)	34 (11%)	20 (4%)
>1 BCC at first diagnosis date	Yes	132 (12%)	69 (24%)	26 (9%)	37 (8%)

Abbreviations: BCC, basal cell carcinoma; BMI, body mass index; IQR, interquartile range.

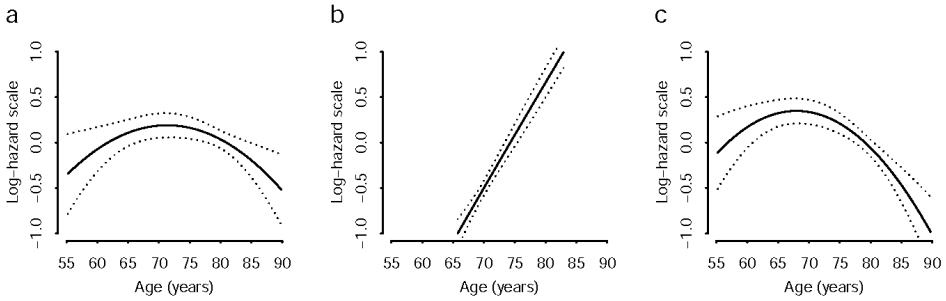


Figure 1. Relationships between age at first BCC diagnosis and risk of a second BCC or death (**a**) *Cause-specific hazard of second BCC.* Nonlinear relation between age at first BCC (x axis) and the logarithmic transformation of the cause-specific hazard of developing a second BCC (y axis) using a Cox model. The dotted lines represent the 95% confidence intervals. (**b**) *Cause-specific hazard of death.* Linear relation between age at first BCC (x axis) and the logarithmic transformation of the cause-specific hazard of dying (y axis) using a Cox model. The dotted lines represent the 95% confidence intervals. (**c**) *Subdistribution hazard of second BCC.* Non-linear relation between age at first BCC (x axis) and the logarithmic transformation of the subdistribution hazard of developing a second BCC (y axis) using a Fine and Gray model. The dotted lines represent the 95% confidence intervals. BCC, basal cell carcinoma.

borderline significant associations with an increased risk of a new BCC, namely male sex, easily sunburned, and truncal localization of the first BCC. In contrast, an increase in coffee consumption of 3 cups per day (HR: 0.8, 95% CI: 0.6–1.0) was borderline significantly associated with a decreased risk of a second BCC.

After backward selection, five predictors remained in the reduced multivariable model: age at first BCC, sex, coffee consumption, superficial subtype of the first BCC, and more than one BCC at first date of diagnosis (Table 2). None of the UVR-related predictors were associated with a second BCC. Being "easily sunburned" also lost its significance after adjustment for all other predictors. The strongest predictor was having more than one BCC at first date of diagnosis (adjusted HR: 2.5, 95% CI: 1.9–3.3). Coffee consumption remained significantly associated with a decreased risk of a second BCC (adjusted HR: 0.7, 95% CI: 0.6–0.9). A complete case analysis on 567 participants resulted in the same reduced multivariable model and comparable HRs (data not shown).

The apparent concordance index (c-index) of the multivariable model was 0.66 (95% CI: 0.58–0.73) at 1 year, 0.67 (95% CI: 0.62–0.72) at 3 years, and 0.65 (95% CI: 0.61–0.69) at 5 years after first BCC diagnosis. After correction for optimism, the c-index of the model was 0.64 at 1 year, 0.65 at 3 years, and 0.63 at 5 years after first BCC diagnosis. When using the score chart for predictions, the apparent c-indices were nearly identical to those of the original model (0.65 at 1 year, 0.67 at 3 years, and 0.65 at 5 years after first BCC diagnosis).

Table 2. Associations between predictors and occurrence of a second BCC (n=293) using the Fine and Gray model for competing risks

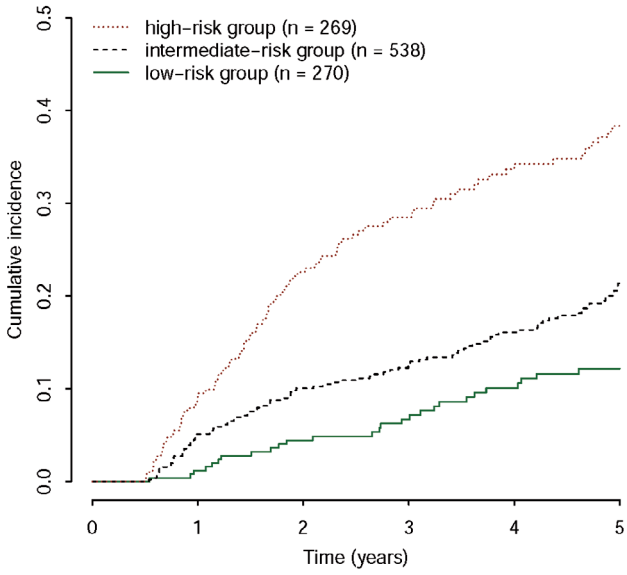
Patient and tumor characteristics	Coding	Univariable models		Multivariable model[1]
Age at first BCC (years)	68 versus 81[2]	1.6 (1.3-2.0)	***	1.6 (1.3-2.0)
Sex	Male	1.3 (1.0-1.6)	*	1.2 (0.9-1.5)
BMI (kg/m2)	24 versus 29[2]	1.1 (0.9-1.3)		-
Pigment status	Dark	Reference		-
	Intermediate	1.2 (0.8-1.6)		-
	Light	1.4 (0.9-2.0)		-
Easily sunburned	Yes	1.3 (1.0-1.6)		-
Outdoor work	Yes	1.1 (0.8-1.5)		-
Sun protection	No or almost never	0.9 (0.7-1.2)		-
Smoking	Ever	1.1 (0.8-1.3)		-
Alcohol consumption (glasses/week)[3]	10 versus 0[2]	1.1 (0.8-1.6)		-
Coffee consumption (cups/day)	5 versus 2[2]	0.8 (0.6-1.0)	*	0.7 (0.6-0.9)
Localization of first BCC	Head	Reference		-
	Extremities	1.1 (0.8-1.5)		-
	Trunk	1.3 (1.0-1.7)	*	-
Superficial first BCC	Yes	1.5 (1.1-2.0)	**	1.3 (0.9-1.7)
>1 BCC at first diagnosis date	Yes	2.6 (2.0-3.4)	***	2.5 (1.9-3.3)

Abbreviations: BCC, basal cell carcinoma; BMI, body mass index.
The baseline cumulative subdistribution hazard is 0.035 at 1 year, 0.106 at 3 years, and 0.170 at 5 years.
* P-value <0.05, **P-value <0.01, and ***P-value <0.001.
[1] After backward selection.
[2] Interquartile range.
[3] Truncated at 10 glasses per week.

Clinical application

The observed cumulative incidence curve of the high-risk group showed a distinct pattern compared with the observed cumulative incidence curves of the other risk groups (Figure 2). Table 3 shows the score chart that was based on the shrunken regression coefficients of the final prediction model; the estimated shrinkage factor was 0.88. Using the score chart, the physician can easily calculate the predicted risk of a second BCC for a patient currently having a first BCC. The patient obtains a score for each predictor, and these are added up to form a total score. The corresponding predicted risks of a second BCC (within 1, 3, and 5 years) can be found in Table 3 as well. For example, a 63-year-old (two points, when age is rounded to 65 years) man (one point) who drinks no coffee (two points) presenting with one (zero points)

superficial (one point) BCC has a total score of 6, which corresponds to a 3-year risk of 21%.



Numbers at risk				
High−risk	269	223	144	92
Intermediate−risk	538	466	348	248
Low−risk	270	222	142	80

Figure 2. Observed cumulative incidence curves of the three risk groups
Observed cumulative incidence (y axis) curves of the three risk groups (low, intermediate, and high-risk) with follow-up time (x axis) using the 25th and 75th percentiles of the risk score distribution as cut points. Below the figure are the numbers at risk at start of follow-up and at 1, 3, and 5 years of follow-up for each risk group.

Table 3. On the left, score chart for predicting an individual's risk of a second BCC at the time of a first BCC. On the right, total scores and corresponding absolute risks of a second BCC at the time of a first BCC

Predictor	Value	Score
Age at first BCC[1] (years)	≤ 55	0
	60	1
	65	2
	70	2
	75	1
	80	0
	85	-3
	≥ 90	-5
Sex	Female	0
	Male	1
Daily intake of cups of coffee	0	2
	1	1
	2	1
	3	0
	4	-1
	5	-1
	≥ 6	-2
Superficial subtype of first BCC	No	0
	Yes	1
> 1 BCC at first date of diagnosis	No	0
	Yes	5
Total score		…

Total score	1-year risk	3-year risk	5-year risk
≤ -5	1%	4%	6%
-4	2%	5%	8%
-3	2%	6%	9%
-2	2%	6%	10%
-1	2%	7%	11%
0	3%	9%	13%
1	3%	10%	16%
2	4%	11%	18%
3	5%	13%	20%
4	5%	15%	23%
5	6%	18%	28%
6	8%	21%	32%
≥ 7	10%	27%	40%

Abbreviation: BCC, basal cell carcinoma.
The predicted risk (%) of a second BCC within 1 year after the primary BCC was determined by: $P = [1-(\exp(-\exp(B) \times 0.035))] \times 100\%$, where
$B = 0.285 \times \text{age} - 0.002 \times \text{age}^2 + 0.152$ (if male sex) $- 0.093 \times$ coffee cups per day $+ 0.209$ (if superficial subtype) $+ 0.796$ (if more than one BCC).

DISCUSSION

This prospective population-based cohort study shows that the absolute risk of a second BCC could be predicted with reasonable accuracy using simple phenotypic, lifestyle and tumor-specific characteristics. The strongest predictor of a second BCC in time was having more than one BCC at initial BCC diagnosis. Participants were 2.5-fold more likely to develop a new BCC compared with individuals who only had one BCC at the initial date of diagnosis. From the concept of field cancerization, this observation is

expected. It is consistent with the results from the Skin Cancer Prevention Study Group and a retrospective Spanish study demonstrating that the total number of prior BCCs was strongly associated with the risk of metachronous BCCs (Karagas et al., 1992; Graells, 2004).

A superficial subtype of the first BCC gave a participant a significantly higher (+30%) risk to develop a second BCC, which is in accordance with data from a British retrospective cohort study (Lovatt et al., 2005). In previous studies, the histopathological subtype of a BCC has also been associated with tumor localization, as most of the truncal BCCs are superficial, and most of the head and neck BCCs are nodular (Bastiaens et al., 1998; Scrivener et al., 2002). We noted a similar pattern, suggesting a good validity of these predictors.

A nonlinear (parabolic) relationship between age at first BCC diagnosis and the risk of a second BCC was detected. As expected, the risk of a second BCC increased with age, but this risk decreased after approximately 68 years of age. Several other cohort studies have shown a similar risk increase with age but not a risk decrease as patients get even older. Reasons could be that they analyzed a younger cohort and/or changed age into a categorical variable so that a possible nonlinear relationship was hidden (Karagas et al., 1992; Richmond-Sinclair et al., 2010; Flohil et al., 2011).

After adjusting for other factors in the multivariable model, male gender was a modest prognostic factor for a second BCC. Other cohorts demonstrated weak to strong relations between male sex and risk of a subsequent BCC, but they did not adjust for tumor characteristics, such as histological subtype and/or localization, that differ across gender (Karagas et al., 1992; Richmond-Sinclair et al., 2010; Flohil et al., 2011).

Remarkably, coffee consumption reduced the risk of a second BCC (adjusted HR per increase in three cups per day: 0.7, 95% CI: 0.6–0.9). Although caffeinated and decaffeinated coffee consumers could not be differentiated in the overall population, ~ 90% of the coffee consumers in RS-I, which accounts for most of the included participants, used caffeinated coffee. Several observational studies investigated the association between coffee intake and BCC development. Recently, a large prospective follow-up study from Australia showed protective effects of coffee consumption (Miura et al., 2014), whereas two European case–control studies did not find a significant association with BCC development (Corona et al., 2001; Milan et al., 2003). Animal studies have shown that oral and topical administration of caffeine inhibit UVB-induced carcinogenesis and selectively increase apoptosis in squamous cell carcinomas (Huang et al., 1997; Lu et al., 2002). In vitro research on human keratinocytes has demonstrated that this inhibitory effect of caffeine may be due to the induction of apoptosis in UVB-damaged keratinocytes (Heffernan et al., 2009; Han et al., 2011). However, people consuming more coffee may also differ from those drinking less coffee for which the analyses were unable to adjust for (i.e., residual confounding). A recent review argues

that coffee intake reflects an, often unmeasured, healthy life style and is indirectly associated with multiple health outcomes (Mirza et al., 2014).

It is interesting that no significant influence was found for pigment status and UVR-related characteristics (easily sunburned, outdoor work, and sun protection) on the development of a second BCC. The lack of this association was consistent with earlier studies (Lovatt et al., 2005; Richmond-Sinclair et al., 2010). A reason for this apparently paradoxical observation could be the so-called index event bias (Dahabreh and Kent, 2011). UVR is a strong risk factor for a first BCC, and participants who have been exposed to high levels of UVR could have a relatively favorable risk factor profile with respect to the other known and unknown risk factors for a first BCC. This relatively favorable risk profile could, with respect to the other risk factors in the statistical analysis, show a seemingly nonsignificant or an even protective relation with the development of a new BCC within this group with high UVR exposure compared with the group without high levels of UVR exposure.

The prediction model and simple score chart allow for identification of high-risk patients for more intensive follow-up, while excluding the low-risk patients from subsequent follow-up visits. This will lower the strain that the group of BCC patients is putting on the limited (specialized) health care. In addition, an earlier detection of BCCs most likely leads to smaller tumor sizes, which in turn will reduce treatment-related morbidity and costs (Mudigonda et al., 2010). Our 1-year (0.64), 3-year (0.65), and 5-year (0.63) discriminative ability is far from perfect, which suggests that other (unknown) predictors also have a role in the development of a second BCC. Combining genetic and non-genetic predictors into one model might increase the c-index.

Limitations

Cohort members may have developed BCCs prior to the complete national coverage of the pathology database (PALGA) in 1991, leading to misclassification bias, which reduces the generalizability. However, between 1971 and 1991 partial coverage was achieved and the mean age of the included participants in 1991 was 61 years, which is seven years younger compared with the mean BCC age of diagnosis (Arits et al., 2011), suggesting that the impact of this bias is at most modest. In addition, approximately 30% of the participants with a first BCC developed at least a second BCC, which is in line with another Dutch PALGA study and a recent meta-analysis (Flohil et al., 2011; Flohil et al., 2013b), suggesting excellent internal validity of the study design.

Because we obtained our BCC cases through a linkage with PALGA, we have missed BCC diagnoses that were not made based on histopathology. However, a recent study showed that only a small percentage (ca. 7%) of patients with metachronous BCCs had subsequent non-histologically confirmed BCCs (Flohil et al., 2013c). In addition, the evidence-based guideline regarding BCC from the Dutch Society for Dermatology

and Venereology (NVDV) states that all biopsied/excised BCCs should be sent for a histopathological diagnosis (http://www.nvdv.nl/wp-content/uploads/2014/08/Richtlijn-Basaalcelcarcinoom-2014.pdf).

The UVR-related items in the questionnaires for this study may not have been optimal but probably picked up major differences in UVR exposure between participants. Although lifestyle characteristics may change over a lifetime, we only measured UVR-related variables, smoking, alcohol consumption, coffee consumption, and BMI at baseline for most participants. However, we do not believe that non-UVR-related behavior changes after a first BCC diagnosis, as most patients do not associate predictors such as smoking, alcohol consumption, and coffee consumption with BCC development. UVR-related behavior may change, but most of the UV damage has already been done years before diagnosis. We did not have UVR exposure information during childhood and adolescence, which is important in the etiopathogenesis of BCC, but because of the potential recall bias this information is often inaccurate (Glanz et al., 2010).

We have tried to find an external cohort for validation of our prediction model (Leiden Skin Cancer Study, Nurses' Health Study and Framingham Heart Study). Unfortunately, multiple BCC data and detailed information on our predictors are scarce.

Conclusion

The risk factor profile for a second BCC differs from that of a first BCC. The strongest predictor is the presentation of multiple BCCs at index date. Other factors associated with a second BCC are age at first BCC, male gender, coffee consumption, and superficial subtype of the first BCC. These simple variables provide a tool to assist physicians to identify high-risk patients, to give a tailored follow-up, and to give information on the risk of subsequent BCCs. External validation and improvement of the discriminative ability are needed.

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