Cumulative incidence and timing of subsequent cutaneous squamous cell carcinomas stratified for patients with organ transplantation and hematologic malignancies: A nationwide cohort study

Celeste J. Eggermont, MD,[a] Loes M. Hollestein, PhD,[a,b] Andrya Hollatz, BSc,[a] Marieke Louwman, PhD,[b] Antien L. Mooyaart, MD, PhD,[c] Tamar Nijsten, MD, PhD,[a] and Marlies Wakkee, MD, PhD[a]

Background: There is lack of nationwide data on the cumulative incidence and timing of subsequent cutaneous squamous cell carcinomas (cSCCs) among patients with a first cSCC.

Objective: To investigate the cumulative incidence and timing of subsequent cSCCs.

Methods: Patients with a first cSCC in 2007/2008 from the Netherlands Cancer Registry were linked to the Netherlands Pathology Registry for subsequent cSCCs and the Netherlands Organ Transplant Registry. Cumulative incidence function curves were calculated for subsequent cSCCs and stratified for immune status.

Results: Among the 12,345 patients, second to sixth cSCC occurred in 4325, 2010, 1138, 739, and 501 patients, with median time intervals of 1.4, 1.2, 0.9, 0.6, and 0.5 years after the previous cSCC, respectively. The cumulative incidence of a subsequent cSCC at 5 years increased from 28% to 67% for the second to sixth cSCC. For solid organ transplant recipients, the cumulative incidences increased from 74% to 92% and from 41% to 64% for patients with hematologic malignancy.

Limitations: Only histopathologically confirmed cSCCs were included.

Conclusion: The risk of a subsequent cSCC steeply rises with the number of prior cSCCs and immune status, while the time interval decreases. This can support more informed decisions about follow-up management. (J Am Acad Dermatol 2024;90:530-6.)

Key words: cancer registry; clinical dermatology; cutaneous squamous cell carcinoma; epidemiology; incidence; hematologic malignancy; oncology; organ transplantation.

INTRODUCTION

With an annual incidence of 2.4 million cases, cutaneous squamous cell carcinoma (cSCC) is among the most common and still rising cancers worldwide, posing a significant burden on many health-care systems.[1,2] Most cSCCs can be cured successfully with surgical excision, but a small proportion of patients experience more aggressive

From the Department of Dermatology, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, the Netherlands[a]; Department of Research and Development, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht, the Netherlands[b]; and Department of Pathology, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, the Netherlands.[c]

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Correspondence to: Marlies Wakkee, MD, PhD, Department of Dermatology, Erasmus MC Cancer Institute, Dr Molewaterplein 40, PO Box 2040, Rotterdam, the Netherlands. E-mail: m.wakkee@erasmusmc.nl.

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behavior, which can result in tumor recurrence, metastasis, and death.[3] Patients with compromised immune systems, such as solid organ transplant recipients (SOTRs) and patients with hematologic malignancy (HM), have a 65- to 250-times higher risk of developing cSCC,[4,5] which are thought to behave more aggressively with higher metastatic potential.[6,7]

Besides the potential but relatively low risk of recurrent or metastatic cSCC, patients are also monitored for early detection of subsequent new cSCCs. Roughly, one-third of patients with an initial cSCC are thought to develop a subsequent cSCC; however, limited information exists related to the frequency and timing of these subsequent cSCCs.[8,9] Having access to more detailed data on the risk of subsequent cSCCs would be valuable to provide more personalized recommendations in terms of follow-up frequency and time intervals.

CAPSULE SUMMARY

- Prior cutaneous squamous cell carcinoma (cSCC) increases the risk of subsequent cSCC, but nationwide data on cumulative risks and timing of subsequent cSCCs are lacking.
- This article demonstrates the opportunity to offer more personalized follow-up schedules for patients with cSCC based on their number of prior cSCCs and immune status.

In contrast to the various studies on the risk of a first primary cSCC, so far only limited research has been conducted on the risk of developing subsequent cSCCs. Two relatively small, retrospective, single-center studies focused on risk factors for one versus multiple cSCCs but did not provide information on the cumulative risks, trends, or time interval of each subsequent cSCC on a population level.[10,11]

Our study therefore aimed to (1) assess the risk of developing subsequent cSCCs up to the sixth cSCC with cumulative incidence function curves, stratified for immune status, and (2) determine the time interval between each subsequent cSCC. We hereto analyzed a nationwide cohort of over 12,000 patients with cSCC from the Netherlands Cancer Registry (NCR) with long-term follow-up, including information on SOTRs and patients with HM.

METHODS

Study population and characteristics

Nationwide data from all patients with a first, histologically verified primary cSCC diagnosed in 2007 or 2008 were retrieved from the Netherlands Cancer Registry (NCR). The study population is an updated cohort that has been previously described by Tokez et al.[7] Data for subsequent cSCC and metastatic cSCC during follow-up were retrieved through linkage with the Nationwide Network and Registry of Histo- and Cytopathology (PALGA),[12] up to August 26, 2020. NCR data contained information on sex, age at first cSCC diagnosis, cSCC topography, follow-up duration, and vital status. The NCR also provided data on HM, including diagnosis date and type of HM. PALGA data contained a complete history of pathology reports with dates of diagnosis for the first and all subsequent cSCCs, as well as corresponding metastasis. Data on SOTRs were obtained through linkage with the Netherlands Organ Transplant Registry (NOTR) and included the date of organ transplantation and organ type.[13] If a patient was either diagnosed with HM or was a SOTR, we defined them as immunocompromised. After linkage, a total of 12,345 patients were included in the study. Ethical approval was obtained from the scientific committees of the NCR, PALGA, and NOTR.

Case definition

To ensure the exclusion of pathology reports related to the same primary in cases of multiple procedures (ie, biopsy and (re)excision) for residual cSCCs, we applied an algorithm based on the registration guidelines of the NCR that incorporates the *International Classification of Diseases for Oncology, third edition (ICD-O-3)*[14] codes for anatomic subsite, lateralization, and a 3-month time frame.[9] A subsequent new primary cSCC was defined as a cSCC located on a different anatomic subsite or lateralization or on the same anatomic subsite and lateralization but at least 3 months after the previous cSCC.

To identify and exclude possible recurrent cSCCs that occurred after this 3-month window, we applied an additional rule-based algorithm based on the free-text conclusion of the pathology reports followed by a manual review.[15] The method of retrieval of metastatic cSCC has been described before.[7] In short, potential cSCC metastases were identified from pathology reports using a combination of PALGA codes and a free-text suggestive for metastases, followed by a manual review. Patients were followed from the first cSCC diagnosis until death or the end of the linkage period, whichever occurred first.

Abbreviations used:

cSCC:	cutaneous squamous cell carcinoma
HM:	hematologic malignancy
ICD-0-3:	*International Classification of Diseases for Oncology, third edition*
IQR:	interquartile range
NCR:	Netherlands Cancer Registry
NOTR:	Netherlands Organ Transplant Registry
PALGA:	Nationwide Network and Registry of Histo- and Cytopathology
SOTR:	solid organ transplant recipient

Statistical analysis

Baseline characteristics of the cohort were analyzed using descriptive statistics and frequency tabulation. We examined each diagnostic interval between subsequent cSCCs separately (ie, first to second, second to third etc.). For each diagnostic interval, we calculated the cumulative incidence of a subsequent cSCC and generated cumulative incidence function curves considering death as a competing event. In cases where a patient presented with multiple primary cSCCs on the same date, we counted each cSCC as an individual primary cSCC and randomly assigned the sequential distribution (ie, the second, the third etc.). Five-year cumulative incidence function curves were stratified for age, sex, organ transplantation, and HM diagnosis. Descriptive statistics were performed using SPSS 28.0 (SPSS Inc), and cumulative incidence function curves were generated using R, version 4.1.2, with the "cmprsk" package.

RESULTS

Study population

Baseline characteristics of the cohort are summarized in Table I. A total of 12,345 patients with a first cSCC in 2007 or 2008 were identified, with a median follow-up of 8.9 years (interquartile range [IQR 3.4-12.3]). The mean age at first cSCC diagnosis was 74.2 years (standard error [SE] 11.5), and 58% of the patients were male. Among all identified patients, 894 patients (7.2%) were immunocompromised, including 250 SOTRs and 674 patients with HM. The majority (70%) received transplantation or were diagnosed with a HM before their first cSCC. Among SOTRs who received their organ transplantation before their first cSCC, nearly one-third (31.0%, n = 67) developed 10 or more cSCCs during follow-up.

Cumulative incidence of subsequent cSCCs

Out of the 12,345 patients, approximately one-third (35.0%, n = 4325) developed at least a second cSCC. Among these patients, 2010, 1138, 739, and 501 developed a subsequent third, fourth, fifth, and sixth cSCC, respectively (Fig 1). The median time intervals between subsequent cSCC diagnoses gradually decreased with each subsequent occurrence: 1.4 years (IQR 0.3-4.4), 1.2 years (IQR 0.6-2.8), 0.9 years (IQR 0.3-2.1), and 0.5 years (IQR 0.2-1.5). After their first cSCC diagnosis, 41.0% (n = 5056) died, with a median survival time of 4.3 years (IQR 1.8-7.7). During the entire follow-up period, 63.1% (n = 7786) died, and 2.0% (n = 250) developed cSCC metastasis.

These numbers resulted in the following 5-year cumulative incidences of subsequent cSCCs: 28% (95% CI 27-28), 42% (95% CI 40-43), 54% (95% CI 52-57), 63% (95% CI 61-66), and 67% (95% CI 64-71) for the second, third, fourth, fifth, and sixth cSCC, respectively (Fig 2). Supplementary Fig 1, available via Mendeley at https://doi.org/10.17632/vmt7dby3rh.1 shows the 10-year cumulative incidence function curves for the 2nd to 10th cSCC. Notably, the 10-year risk of developing a second cSCC (34% [95% CI 34-45]) was comparable to developing a third cSCC after the second (33% [95% CI 32-35]) within only 2.5 years (Supplementary Table I, available via Mendeley at https://doi.org/10.17632/vmt7dby3rh.1).

Cumulative incidence by immune status

Stratification of the cumulative incidence function curves by SOTRs and patients with HM showed an increased risk of subsequent cSCC development among both groups. Among SOTRs, the 5-year cumulative incidence rates of developing a second, third, fourth, fifth, and sixth cSCC were 74% (95% CI 68-79), 83% (95% CI 77-88), 83% (95% CI 76-88), 88% (95% CI 82-93), and 92% (95% CI 86-96), respectively (Fig 3). In contrast, non-SOTRs had a substantially lower 5-year cumulative incidence, with rates of 27% (95% CI 26-27), 40% (95% CI 39-42), 54% (95% CI 51-56), 62% (95% CI 59-65), and 66% (95% CI 61-70) for a second, third, fourth, fifth, and sixth, respectively (Supplementary Fig 2, available via Mendeley at https://doi.org/10.17632/vmt7dby3rh.1).

Among patients with HM, the risk of developing a second cSCC was 41% (95% CI 37-45), which increased to 52% (95% CI 47-58) for a third cSCC (Fig 4). In comparison, non-HM patients had a risk of 27% (95% CI 26-28) for developing a second cSCC, which increased to 41%(95% CI 40-43) for a third cSCC (Supplementary Fig 3, available via Mendeley at https://doi.org/10.17632/vmt7dby3rh.1). The risk of developing a subsequent fourth to sixth cSCC was similar for HM patients and non-HM patients, with rates of 54% (95% CI 47-61), 64% (95% CI 53-73), and 58% (95% CI 44%-69%) for HM patients, respectively,

Table I. Descriptive characteristics of a nationwide cohort of patients with a first primary cutaneous squamous cell carcinoma in 2007/2008 who developed subsequent cSCC during 12-year follow-up period

	No. (%)					
		Number of subsequent cSCCs				
Characteristic	**Overall**	**1 cSCC**	**2 cSCCs**	**3 cSCCs**	**4-9 cSCCs**	**≥10 cSCCs**
Total	12,345	8020	2315	872	953	185
Sex						
Male	7101 (57.5)	4367 (54.4)	1393 (60.2)	556 (63.8)	667 (70.0)	118 (63.8)
Female	5244 (42.5)	3653 (45.5)	922 (39.8)	316 (36.8)	286 (30.0)	67 (36.2)
Age at first diagnosis, mean (SD), years	74.2 (11.5)	74.3 (11.8)	74.9 (10.9)	74.7 (10.0)	73 (10.4)	64.8 (12.2)
Follow-up in the dataset, median (IQR), years	8.9 (3.4-12.3)	8.3 (3.1-12.2)	9.1 (4.3-12.2)	9.7 (5.1-12.4)	10.7 (6.8-12.4)	11.4 (8.1-12.6)
Immunosuppression						
History of organ transplant at first diagnosis date	220 (1.8)	39 (0.5)	25 (1.1)	27 (3.1)	62 (6.5)	67 (36.2)
History of hematologic malignancy at first diagnosis date	399 (3.2)	208 (2.6)	84 (3.6)	51 (5.8)	47 (4.9)	9 (4.9)
Organ transplant after first diagnosis date	30 (0.2)	5 (0.1)	5 (0.2)	3 (0.3)	6 (0.6)	10 (5.4)
Hematologic malignancy after first diagnosis date	275 (2.2)	136 (1.7)	56 (2.4)	35 (4.0)	44 (4.6)	4 (2.2)

cSCC, Cutaneous squamous cell carcinoma; *IQR*, interquartile range; *SD*, standard deviation.

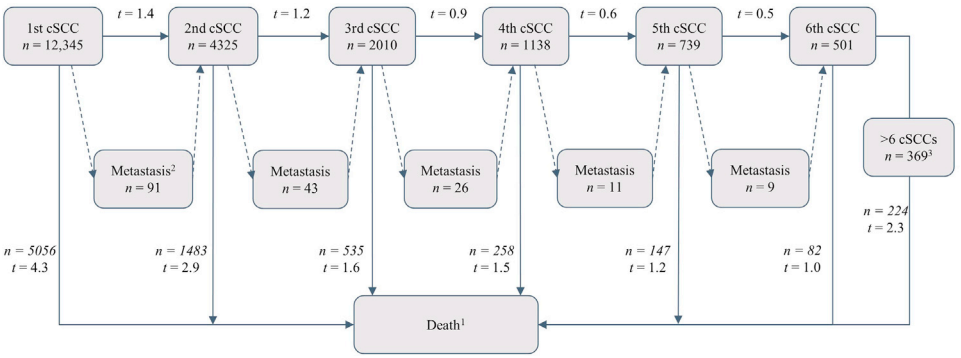
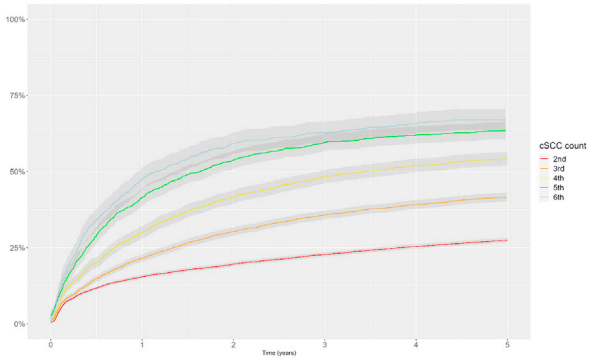


Fig 1. Structure of the data set with numbers of patients (n) per subsequent cutaneous squamous cell carcinoma (cSCC) and median time intervals in years (t) between each subsequent cSCC, up to the sixth cSCC. Censoring due to death occurred for 5056, 1483, 535, 258, 147, and 82 patients after having a first, second, third, fourth, fifth, and sixth cSCC diagnosis date, respectively. [1]Death by any cause. [2]'Metastasis' indicates the occurrence and timing of patients developing metastasis during follow-up, in relation to the sequential number of cSCCs. It runs parallel to a subsequent cSCC, meaning that patients can still develop subsequent cSCCs even after metastasis, as indicated by the *dashed line*. [3]Of all patients with more than 6 cSCCs (n = 369), 224 were dead at the end of follow-up, and the median time to death was of 2.3 years. *cSCC*, Cutaneous squamous cell carcinoma.

and 56% (95% CI 54-59), 66% (95% CI 63-69), and 71% (95% CI 68-75) for non-HM patients, respectively.

Cumulative incidence by sex and age

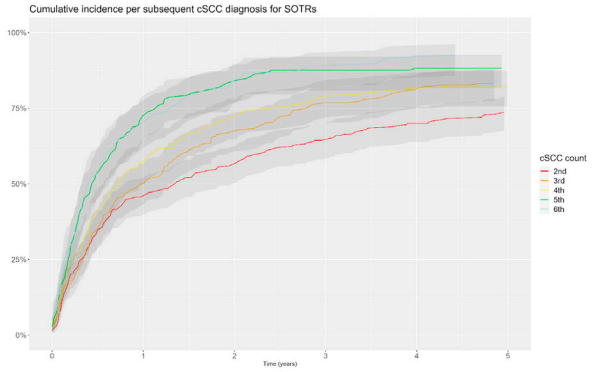
Sex-based analyses revealed that males had a higher risk for a second and third cSCC (31% [95% CI 29-32] and 44% [95% CI 42-46], respectively) than females (23% [95% CI 22-25] and 38% [95% CI 36-41], respectively). There were no differences in subsequent fourth to sixth cSCC between males and females (Supplementary Fig 4, *A* and *B*, available via Mendeley at https://doi.org/10.17632/vmt7dby3rh.1). Patients aged 60 years and older at the time of their first cSCC



Numbers at risk

2nd cSCC	12345	9697	8534	7597	6794	6093
3rd cSCC	4325	3100	2457	1931	1551	1222
4th cSCC	2010	1219	848	557	385	270
5th cSCC	1138	571	357	220	143	84
6th cSCC	739	326	200	116	55	27

Fig 2. Cumulative incidence function curves with 95% CIs for the occurrence of a subsequent cSCC per diagnosis sequence number, from the second until the sixth cSCC diagnosis; curves were truncated at 5 years of follow-up. *cSCC*, Cutaneous squamous cell carcinoma.



Numbers at risk

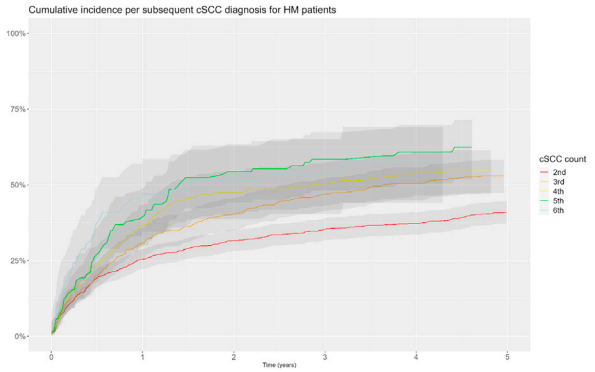
2nd cSCC	250	127	94	68	52	42
3rd cSCC	205	98	59	37	24	16
4th cSCC	175	66	32	18	13	10
5th cSCC	145	35	18	9	6	3
6th cSCC	130	35	16	8	4	3

Fig 3. Cumulative incidence function curves with 95% CIs for the occurrence of a second to sixth cSCC stratified for solid organ transplant recipients; curves were truncated at 5 years of follow-up. *cSCC*, Cutaneous squamous cell carcinoma; *SOTR*, solid organ transplant recipient.

diagnosis showed a slightly higher risk of a second cSCC compared to those younger than 60 years (28% [95% CI 27-29] and 24% [95% CI 22-27], respectively). However, the risk of further subsequent cSCCs was higher in patients younger than 60 years at the time of first cSCC diagnosis, considering the competing risk of death (Supplementary Fig 5, *A* and *B*, available via Mendeley at https://doi.org/10.17632/vmt7dby3rh.1).

DISCUSSION

In this nationwide cohort study, we demonstrated that the number of prior cSCCs is a strong predictor



Numbers at risk

2nd cSCC	674	429	334	277	242	195
3rd cSCC	330	205	148	112	82	56
4th cSCC	190	99	60	38	28	21
5th cSCC	104	51	27	16	10	5
6th cSCC	66	25	11	6	1	0

Fig 4. Cumulative incidence function curves with 95% CIs for the occurrence of a second to sixth cSCC stratified for patients with hematologic malignancy; curves were truncated at 5 years of follow-up. *cSCC*, Cutaneous squamous cell carcinoma; *HM*, hematologic malignancy.

of the risk of a subsequent cSCC, with the risk rising steeply with each subsequent occurrence while the diagnostic time interval gradually decreases. Among SOTRs with an initial cSCC, the risk of a subsequent cSCC was found to be imminent and remarkably high, with a 5-year cumulative incidence of 74%, while this risk was nearly 3 times lower (28%) for immunocompetent patients.

The risk of developing a third to sixth cSCC increased substantially compared with the risk of developing a second cSCC. Our analysis showed that the risk of developing a second cSCC after a first cSCC at 5 years was similar to the risk of developing a third cSCC at 2 years after having had 2 prior cSCCs (28% and 30%, respectively). We also found that, at the end of the 12-year follow-up period, approximately 65% of patients diagnosed with a first cSCC in 2007/2008 had not developed any subsequent cSCC. The overall low risk of metastasis, together with the enormous and increasing burden of follow-up visits on our dermatologic capacity, therefore emphasizes the need to re-evaluate current guideline-based follow-up schedules.[7,16]

Previous studies already mentioned that a history of prior cSCC is the strongest predictor for a subsequent cSCC.[17,18] Our study underscores the value of analyzing the risk after each subsequent cSCC and shows that the risk of further subsequent cSCCs is notably higher than the risk of developing a second cSCC. Moreover, patients with only 1 cSCC have a high probability of 65% of remaining free from any subsequent cSCC throughout their lifetime. The latter observation is also affected by the competing

event of death within an older population at baseline.

Our findings align with the results obtained in the study conducted by Wehner et al[19] on the timing of subsequent new keratinocyte carcinomas (KC), where they observed that the risk for subsequent new KCs over time is lower after a first lifetime KC diagnosis compared to the risk after any subsequent KC. Wehner et al reported higher 5-year cumulative risks compared to our study (~42% for a second cSCC, increasing up to ~61% for a third cSCC). This discrepancy may be attributed to their methodology, as their use of the 1 minus Kaplan-Meier survival method instead of cumulative incidence curves did not account for the competing risk of death, potentially resulting in an overestimation of risk probabilities.[20,21]

Our study also revealed distinct risks for immunocompromised patients. Prior research has identified low-, medium-, and high-risk groups for developing any skin cancer post-transplant.[22] Our study adds to that, showing that once a SOTR has developed a first cSCC, the risk for a second cSCC is remarkably high and occurs within a relatively short time of, on average, 8 months. These findings underscore the need for regular and ongoing follow-up for SOTRs after their first cSCC by transplant physicians, general practitioners, and/or dermatologists. The high risks observed in SOTRs for multiple cSCCs align with other large studies demonstrating a high incidence of multiple cSCCs in this immunocompromised group.[23,24]

Among patients with a HM, we also observed an increased risk of developing a second and third cSCC compared to the general population. The association between HM and the increased risk of skin cancer and more aggressive behaviour has been long reported in the literature,[25,26] but the risk of developing subsequent skin cancers, particularly cSCC, has not yet been investigated. Patients with HM suffer from intrinsically compromised immune surveillance, and treatment-related effects may further amplify this risk.[27,28] The observed convergence in cSCC risk between HM and non-HM patients after a third cSCC may result from immune system recovery after treatment or treatment modification after (subsequent) cSCC development. However, the complex relationship between the type of HM, its treatment, and the development of subsequent cSCCs requires further investigation. Meanwhile, it is important to emphasize that the management and surveillance of cSCC in patients with HM should take into account their increased risk of developing subsequent cSCCs.

This study has several notable strengths. First, the availability of a nationwide cancer registry linked to a nationwide pathology registry and an organ transplant registry, complemented with data on HM over a long study period, allows for robust analyses that are generalizable to light-skinned populations worldwide.

Furthermore, we calculated nationwide cumulative incidences and trends specifically for each subsequent cSCC, while prior studies have mainly focused on risk factors for 1 cSCC versus multiple cSCCs.[10,11]

Nevertheless, several limitations need to be considered. First, to ensure that residual cSCCs were not counted as new primaries, we employed an algorithm based on registration rules within the NCR that considers cSCCs diagnosed on the same body site within 3 months as related to the same primary cSCC. As new primaries can also occur within 3 months, this could have resulted in an underestimation of the true number of new cSCCs per patient.

Second, since our study only included histopathologically confirmed cSCCs, tumors that have been treated without histologic confirmation may have been missed. This proportion is likely to be quite small, as the Dutch cSCC guideline recommends that all excised cSCCs follow histopathologic confirmation.[29]

Finally, due to the use of routinely collected health-care data, we were unable to include data on patient characteristics related to multiple cSCC development, such as sun exposure, (prior) actinic keratosis, family history of skin cancer, and skin phototype. However, the main focus of our study was the cumulative incidence and timing of subsequent cSCCs rather than examining risk factors.

In conclusion, this nationwide cohort study provides valuable insights into the patterns and timing of subsequent cSCC development. It highlights the progressive risk of subsequent cSCC, with even higher risks for SOTRs and patients with HM, while the time interval between occurrences decreases for all patients. While for SOTRs and patients with HM, close follow-up schedules are obvious from the first cSCC onward, the majority of nonimmunocompromised patients with cSCC could benefit from more personalized follow-up schedules, taking into account the number of prior cSCCs and potentially reducing the total volume of follow-up visits.

We extend our gratitude to the registrars of the Netherlands Cancer Registry for their diligent data collection. Additionally, we would like to thank the advisors of PALGA for their assistance with the data extraction and

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Conflicts of interest

Dr Wakkee served as an advisory board member on advanced cSCC for Sanofi Genzyme, and received financial reimbursement for her participation. All other authors declare no conflicts of interest.

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