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Skin cancer risk in more than 200 000 patients with haematological malignancies over 30 years: a nationwide population-based study in the Netherlands

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Abstract

Background Patients with haematological malignancies are at increased risk of developing skin cancer and often experience worse skin cancer-related outcomes. However, there is a lack of nationwide, population-based data with long-term follow-up on the incidence and risks of different skin cancer types across all haematological malignancies.

Objectives To assess population-based risk estimates for cutaneous squamous cell carcinoma (cSCC), malignant melanoma (MM), Merkel cell carcinoma (MCC) and basal cell carcinoma (BCC) among patients with haematological malignancies, stratified by skin cancer type and haematological malignancy subgroup. These estimates can serve as a base for surveillance guidelines and patient education.

Methods This nationwide population-based epidemiological cohort study used data from 210 794 patients diagnosed with a haematological malignancy between 1989 and 2020 from the Netherlands Cancer Registry (NCR). In addition, data on each type of histopathologically confirmed skin cancer per patient after haematological malignancy diagnosis were retrieved from the NCR. Patients with a history of skin cancer prior to their haematological malignancy were excluded. Cumulative incidences, standardized incidence ratios (SIRs) and absolute excess risks for each of the four skin cancers were calculated and stratified by haematological malignancy subgroup, age, sex, follow-up and primary treatment.

Results The overall 10-year cumulative incidence of developing a first skin cancer was 2.6% for cSCC, 0.5% for MM, 0.05% for MCC and 4.8% for BCC. Compared with the general population, nearly all haematological malignancy subgroups showed more than a twofold increased risk of cSCC, MM, MCC and BCC. Patients with chronic lymphocytic leukaemia (CLL) showed the highest risks for each of the four skin cancers, with SIRs of 4.4 for cSCC, 2.7 for MM, 9.3 for MCC, and 2.6 for BCC. These elevated risks persisted for > 30 years after haematological malignancy diagnosis.

Conclusions Patients with all types of haematological malignancies, and especially those with CLL, have a lifetime increased risk of developing different types of skin cancer. These findings highlight the importance of creating awareness among patients and care providers about this increased risk and promoting sun-protective measures and regular skin self-examinations in this high-risk population.

Lay summary

Due to advances in treatment, the life expectancy of people with blood cancers has improved. Therefore, it is important to understand the long-term health risks in these patients. This includes the risk of second cancers later in life. Skin cancer is the most common second cancer in patients with a blood cancer. A skin cancer called 'basal cell carcinoma' is the most common skin cancer diagnosis in the Netherlands. This is followed by another type called 'cutaneous squamous cell carcinoma'. Melanoma is a less common type of skin cancer and Merkel cell carcinoma is even rarer.

We looked at the risks of these four skin cancers in people after they were diagnosed with a blood cancer. Using data from the Netherlands Cancer Registry, we calculated the risks of skin cancers in patients with a blood cancer over 31 years (up to 2021). People with nearly all types of blood cancer had twice the risk of developing each of the four skin cancers than the general population. People with a type of blood cancer called 'chronic lymphocytic leukaemia' had the highest risk of developing a skin cancer.

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Our results show that patients and doctors need to know about the lifelong risk of skin cancer. As most skin cancers can be prevented, it is important for patients to protect their skin from the sun. They should also perform regular self-skin checks to detect cancers at an early stage.

What is already known about this topic?

- Skin cancer is the most common second primary malignancy in patients with haematological malignancies.
- Patients with haematological malignancies often experience more aggressive behaviour of their skin cancers, leading to poorer outcomes.
- There is a lack of nationwide, population-based data with long-term follow-up on the incidence and risk of different skin cancer types across all haematological malignancies.

What does this study add?

- Patients with all types of haematological malignancies have high relative and absolute risks of developing cutaneous squamous cell carcinoma, malignant melanoma, Merkel cell carcinoma and basal cell carcinoma, with the highest risks found in those with chronic lymphocytic leukaemia.
- These risks persist for over 30 years after diagnosis.
- Our findings underscore the need for increased awareness, sun-protective measures and long-term surveillance in this high-risk population.

The continuous improvement in the life expectancy of patients with haematological malignancies is offset by an increased risk of developing second primary malignancies, such as skin cancer.[1–4] Skin cancer is among the most common second primary malignancies, especially in patients with chronic lymphocytic leukaemia (CLL), with a disproportionately higher risk of cutaneous squamous cell carcinoma (cSCC), malignant melanoma (MM) and Merkel cell carcinoma (MCC) compared with basal cell carcinoma (BCC).[5–7] These skin cancers also seem to behave more aggressively in patients with haematological malignancies, leading to worse outcomes.[7,8] Although several population-based studies have investigated the association between haematological malignancies and skin cancer, most included a relatively small number of patients with short follow-up durations and primarily focused on all types of non-Hodgkin lymphoma (NHL) combined or CLL specifically.[9–11] Few have examined specific NHL subtypes or evaluated cSCC, MM, MCC and BCC separately.[12,13]

A recent Dutch study of 25 000 patients with CLL reported a 63% higher risk [standardized incidence ratio (SIR) 1.63, 95% confidence interval (CI) 1.59–1.68] of any second primary malignancy vs. the general Dutch population.[6] Specifically for cSCC, the risk was nearly fivefold and more than twofold for MM.[6] There is a lack of nationwide population-based studies with long-term follow-up on the incidence of the four most common skin cancers in patients with haematological malignancies (i.e. cSCC, MM, MCC and BCC) stratified by skin cancer type and haematological malignancy subgroup.

A reasonable estimate of the skin cancer risk distribution among all subgroups of haematological malignancies is essential to improve patient care, including developing optimal surveillance strategies and minimizing skin cancer-associated morbidity and mortality. Therefore, we used nationwide cancer registry data over a period of > 30 years to assess robust risk estimates for the four most common skin cancer types across all haematological malignancy subgroups in the Netherlands.

Materials and methods

Study setting

All histopathologically confirmed malignancies in the Netherlands have been registered in the Netherlands Cancer Registry (NCR) since 1989. The NCR relies on comprehensive case notification via the nationwide Network of Histopathology and Cytopathology (Palga) and the National Registry of Hospital Discharges (i.e. inpatient and outpatient discharges). Completeness of registration is > 95% for haematological and 93% for cutaneous malignancies, excluding BCCs.[14] BCCs were initially registered by a regional population-based registry [i.e. Eindhoven Cancer Registry (ECR)], which is part of the NCR, between 1989 and 2016. Since mid-2016, all BCCs, including multiple BCCs per patient, are registered nationwide in the NCR through automatic case ascertainment from Palga.[15]

Study design and data sources

We included all patients diagnosed with a haematological malignancy between 1989 and 2020 from the NCR. Additionally, data on each type of histopathologically confirmed primary skin cancer per patient (i.e. cSCC, BCC, MM and MCC) after primary haematological malignancy diagnosis were obtained. Patients with a history of any skin cancer before their haematological malignancy were excluded (n = 7451/218 245; 3.4%).

We retrieved data on age, sex, morphology, topography and initial treatment for haematological malignancies. Vital status (i.e. alive, dead or emigrated) was obtained through linkage with the Nationwide Population Registries Network. Topography and morphology were coded according to the International Classification of Diseases for Oncology, Third Edition (Tables S1, S2; see Supporting Information).[16] Nationwide aggregated data on skin cancer incidence among the general population was retrieved to compare

risks between patients with haematological malignancies and the general population.

From the NCR, we retrieved data from all patients with newly diagnosed cSCC, MM and MCC between 1989 and 2020. For BCC, we retrieved data on BCC incidence between 1989 and mid-2016 from the ECR and between mid-2016 and 2020 from the NCR. To ensure consistency throughout the study period, we limited BCC analyses to the population of the ECR for the entire timespan of the study (1989–2020).

Measures, definitions and outcomes

Cumulative incidence

The cumulative incidence of the development of skin cancer was calculated for each of the four skin cancers up to 31 years after haematological malignancy diagnosis, taking into account the competing risk of death. Cumulative incidence curves were stratified for all haematological malignancy subgroups. Additionally, a sensitivity analysis was conducted that included patients with a history of any skin cancer prior to their haematological malignancy diagnosis.

Standardized incidence ratios and absolute excess risks

The SIRs for each of the four skin cancers were calculated by dividing the number of observed skin cancers by the number of expected skin cancers from the general population. The expected number of skin cancers was obtained by multiplying sex-, age- (5-year intervals) and calendar year-specific (1-year intervals) incidence rates from the NCR by the accumulated person-years (PY) at risk. PY at risk were calculated from the date of haematological malignancy diagnosis until each first skin cancer diagnosis, death or end of follow-up (31 December 2020), whichever occurred first. Patients who developed multiple types of skin cancer after a haematological malignancy diagnosis were considered for each skin cancer type individually.

The absolute excess risk (AER), expressed per 10 000 PY, was calculated as the difference between the observed and expected number of skin cancers, divided by the PY at risk. SIRs and AERs were presented overall, according to sex, age group (< 60 years, 60–74 years and ≥ 75 years), follow-up period (0–1 year, 2–5 years, 6–10 years and 11–30 years after haematological malignancy diagnosis), primary treatment at time of diagnosis (no treatment, radiotherapy monotherapy, systemic treatment monotherapy and stem cell transplantation) and according to all haematological malignancy subgroups. We assigned 95% CIs for the SIRs by assuming a Poisson distribution for the number of observed skin cancers and used the criteria of nonoverlapping CIs to demonstrate statistically significant differences between subgroups.[17] Statistical analyses were performed with SPSS 28.0 (IBM, Armonk, NY, USA) and R version 4.3.1 ('cmprsk', 'lexpand', 'Epi' and 'PopEpi' packages; R Foundation for Statistical Computing, Vienna, Austria). The STROBE reporting guideline was followed.[18]

Results

Study population

The NCR data included 210 794 patients diagnosed with a haematological malignancy between 1989 and 2020, all without a history of skin cancer. Median age at diagnosis was 68 years [interquartile range (IQR) 56–76] and 56% (n = 118 197/210 794) were men (Table 1). The median duration of follow-up was 4.2 years (IQR 1.1–9.3). The most common haematological malignancies included diffuse large B-cell lymphoma (16%; n = 33 331/210 794), multiple myeloma (14%; n = 29 593/210 794) and CLL (12%; n = 24 664/210 794). At diagnosis, nearly half (49%; n = 103 964/210 794) of the patients received systemic treatment and 5% (n = 10 801/210 794) underwent haematopoietic stem cell transplantation (HSCT). Regional data from the ECR, used for BCC analyses, included 23 608 patients diagnosed with a haematological malignancy between 1989 and 2020. There were no significant differences in patient demographics and treatment characteristics compared with the NCR data (Table S3).

During follow-up, 5802 patients developed a first cSCC, 1187 patients developed MM, 111 patients developed MCC and 1040 patients (out of a total of 23 608 patients) developed BCC (Table 2). The median time from haematological malignancy diagnosis to first skin cancer diagnosis ranged from 4 to 7 years. CLL was the most frequent underlying haematological malignancy in patients who developed skin cancer (Table 2).

Table 1 Demographics and characteristics of the primary treatment of patients diagnosed with a haematological malignancy in the Netherlands, 1989–2020 (n = 210 794)

Characteristic	*n* (%)
Sex	
Male	118 197 (56)
Female	92 597 (44)
Age at haematological malignancy diagnosis (years), median (IQR)	68 (56–76)
Duration of follow-up (years), median (IQR)	4.2 (1.1–9.3)
Haematological malignancy subgroups	
Acute myeloid leukaemia	17 746 (8)
Chronic lymphocytic leukaemia	24 664 (12)
Chronic myeloid leukaemia	4918 (2)
Classical Hodgkin lymphoma	10 563 (5)
Diffuse large B-cell lymphomas	33 331 (16)
Essential thrombocythaemia/polycythaemia vera	13 475 (6)
Follicular lymphomas	14 155 (7)
Indolent non-Hodgkin lymphomas, other	8487 (4)
Lymphoma, NOS	7702 (4)
Lymphoplasmacytic lymphoma	6826 (3)
Mantle-cell lymphoma	4523 (2)
Mature T- and NK-cell neoplasms (excl. skin)	5336 (3)
Multiple myeloma	29 593 (14)
Myelodysplastic syndrome	12 761 (6)
Myelodysplastic/myeloproliferative neoplasms, other	5359 (3)
Other[a]	11 355 (5)
Treatment at haematological malignancy diagnosis	
No treatment	85 385 (41)
Systemic treatment	103 964 (49)
Radiotherapy alone	10 644 (5)
Haematopoietic stem cell transplantation	10 801 (5)

Data are presented as n (%) unless otherwise stated. IQR, interquartile range; NK, natural killer; NOS, not otherwise specified. [a]Other haematological malignancy subgroups include biphenotypic acute leukaemia (n = 118, < 0.1%); Burkitt lymphoma (n = 1002, 0.5%); cutaneous neoplasms (n = 4462, 2%); histiocytic/dendritic neoplasm (n = 368, 0.2%); Hodgkin lymphoma, nodular lymphocyte predominant (n = 805, 0.4%); leukaemia, NOS (n = 77, < 0.1%); lymphoblastic leukaemia/lymphoblastic lymphoma (n = 2841, 1.3%); plasma cell neoplasms, other (n = 1682, 0.8%).

Table 2 Characteristics of different skin cancer types in patients with haematological malignancies in the Netherlands, 1989–2020

	Nationwide (n=210 794)[a]						Regional (n=23 608)[b]	
	cSCC (n=5802)		MM (n=1187)		MCC (n=111)		BCC (n=1040)	
Characteristic	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
n (%)	3996 (69)	1806 (31)	711 (60)	476 (40)	63 (57)	48 (43)	652 (63)	388 (37)
Age at haematological malignancy diagnosis (years), median (IQR)	70 (63–76)	71 (63–78)	65 (56–72)	65 (54–73)	69 (60–75)	70 (67–76)	67 (60–73)	67 (59–74)
Follow-up duration (years), median (IQR)	9 (6–14)	10 (6–15)	10 (6–15)	11 (7–17)	11 (5–16)	8 (5–14)	11 (7–16)	12 (7–17)
Time to skin cancer diagnosis (years), median (IQR)	5.1 (2.4–9.0)	5.5 (2.6–9.8)	4.8 (2.1–9.4)	5.1 (2.4–9.5)	7.1 (3.2–10.9)	5.7 (3.3–10.0)	4.8 (2.1–9.0)	4.7 (2.3–9.2)
Haematological malignancy subgroup								
AML	72 (2)	32 (2)	9 (1)	17 (4)	3 (5)	0 (0)	9 (1)	4 (1)
CLL	1218 (30)	455 (25)	198 (28)	99 (21)	24 (38)	22 (46)	181 (28)	91 (23)
CML	67 (2)	43 (2)	17 (2)	12 (3)	0 (0)	1 (2)	9 (1)	5 (1)
CHL	89 (2)	37 (2)	31 (4)	29 (6)	5 (8)	0 (0)	29 (4)	33 (9)
DLBCL	474 (12)	248 (14)	90 (13)	51 (11)	7 (11)	7 (15)	80 (12)	43 (11)
ET/PCV	313 (8)	208 (12)	48 (7)	49 (10)	2 (3)	4 (8)	52 (8)	36 (9)
FLs	279 (7)	158 (8)	46 (6)	43 (9)	5 (8)	1 (2)	55 (8)	44 (11)
Indolent NHL, other	209 (5)	93 (5)	53 (7)	24 (5)	6 (10)	1 (2)	34 (5)	12 (3)
Lymphoma, NOS	184 (5)	83 (5)	31 (4)	19 (4)	1 (2)	1 (2)	36 (6)	16 (4)
LPL	214 (5)	82 (5)	28 (4)	18 (4)	2 (3)	2 (4)	26 (4)	18 (5)
Mantle-cell lymphoma	93 (2)	29 (2)	15 (2)	10 (2)	3 (5)	0 (0)	17 (3)	5 (1)
Mature T- and NK-cell neoplasms (excl. skin)	52 (1)	20 (1)	5 (1)	7 (1)	1 (2)	1 (2)	9 (1)	7 (2)
Multiple myeloma	312 (8)	131 (7)	53 (7)	54 (11)	2 (3)	5 (10)	51 (8)	34 (9)
MDS	196 (5)	93 (5)	20 (3)	14 (3)	0 (0)	1 (2)	25 (4)	13 (3)
Myelodysplastic/ myeloproliferative neoplasms, other	100 (3)	29 (2)	21 (3)	6 (1)	2 (3)	1 (2)	20 (3)	10 (3)
Other[c]	124 (3)	65 (4)	46 (6)	24 (5)	0 (0)	1 (2)	19 (3)	17 (4)
Age at first skin cancer diagnosis (years)								
< 60	676 (17)	293 (16)	228 (32)	179 (38)	16 (25)	5 (10)	158 (24)	102 (26)
60–74	2096 (52)	852 (47)	338 (48)	199 (42)	31 (49)	26 (54)	355 (54)	198 (51)
≥ 75	1224 (31)	661 (37)	145 (20)	98 (21)	16 (25)	17 (35)	139 (21)	88 (23)
Latency period (years)[d]								
(+) 0–1	826 (21)	359 (20)	182 (26)	106 (22)	14 (22)	9 (19)	153 (23)	85 (22)
(+) 2–5	1468 (37)	602 (33)	255 (36)	160 (34)	14 (22)	17 (35)	235 (36)	152 (39)
(+) 6–10	1028 (26)	478 (26)	149 (21)	118 (25)	21 (33)	13 (27)	142 (22)	76 (20)
(+) 11–30 years	674 (17)	367 (20)	125 (18)	92 (19)	14 (22)	9 (19)	122 (19)	75 (19)
Treatment at haematological malignancy diagnosis								
No treatment	1947 (49)	858 (48)	335 (47)	205 (43)	27 (43)	25 (52)	321 (49)	173 (45)
Radiotherapy alone	149 (4)	90 (5)	52 (7)	33 (7)	1 (2)	1 (2)	42 (6)	45 (12)
Systemic treatment alone	1764 (44)	804 (45)	301 (42)	213 (45)	33 (52)	22 (46)	273 (42)	160 (41)
HSCT	136 (3)	54 (3)	23 (3)	25 (5)	2 (3)	0 (0)	16 (2)	10 (3)

Data are presented as n (%) unless otherwise stated. AML, acute myeloid leukaemia; BCC, basal cell carcinoma; CLL, chronic lymphocytic leukaemia; CHL, classical Hodgkin lymphoma; cSCC, cutaneous squamous cell carcinoma; DLBCL, diffuse large B-cell lymphoma; ET, essential thrombocythaemia; F, female; FL, follicular lymphoma; IQR, interquartile range; LPL, lymphoplasmacytic lymphoma; M, male; MCC, Merkel cell carcinoma; MDS, myelodysplastic syndromes; MM, malignant melanoma; NHL, non-Hodgkin lymphoma; NK, natural killer; NOS, not otherwise specified; PCV, polycythaemia vera. [a]All analyses related to cSCC, MM and MCC were performed on a national level (n=210,794) as these skin cancers have been recorded by the National Cancer Registry since 1989. [b]BCC analyses were limited to the population covered by the Eindhoven Cancer Registry (ECR), as BCC records prior to 2016 were exclusively recorded by the regional ECR, with nationwide registration starting in mid-2016. [c]Other haematological malignancy subgroups include biphenotypic acute leukaemia; Burkitt lymphoma; cutaneous neoplasms; histiocytic/dendritic neoplasm; Hodgkin lymphoma, nodular lymphocyte predominant; leukaemia, NOS; lymphoblastic leukaemia/lymphoblastic lymphoma; and plasma cell neoplasms, other. [d]The latency period is defined as the time from haematological malignancy diagnosis to the diagnosis of skin cancer.

Cumulative incidence

The 10-year cumulative incidence of a first cSCC, MM, MCC and BCC was 2.5% (95% CI 2.4–2.6), 0.5% (95% CI 0.5–0.5), 0.05% (95% CI 0.04–0.06) and 4.0% (95% CI 3.7–4.3), respectively (Figure 1). These rates nearly doubled over 30 years, with cumulative incidences of 4.4% (95% CI 4.3–4.5) for cSCC and 7.3% (95% CI 6.7–7.9) for BCC. As patients with a history of a skin cancer have a higher risk of developing another skin cancer, we performed a sensitivity analysis including patients with a history of any skin cancer prior to their haematological malignancy. However, as patients with a history of skin cancer comprised only 3.4% (n=7451/218 245) of the total cohort size, this analysis showed no changes for CSCC, MM and MCC. For BCC, the 30-year cumulative incidence increased slightly (8.1%, 95% CI 7.5–8.7) (Table S4; see Supporting Information).

Detailed cumulative incidences stratified by haematological malignancy subgroup are provided in Figures S1–S4 and Tables S5–S8 (see Supporting Information). In these

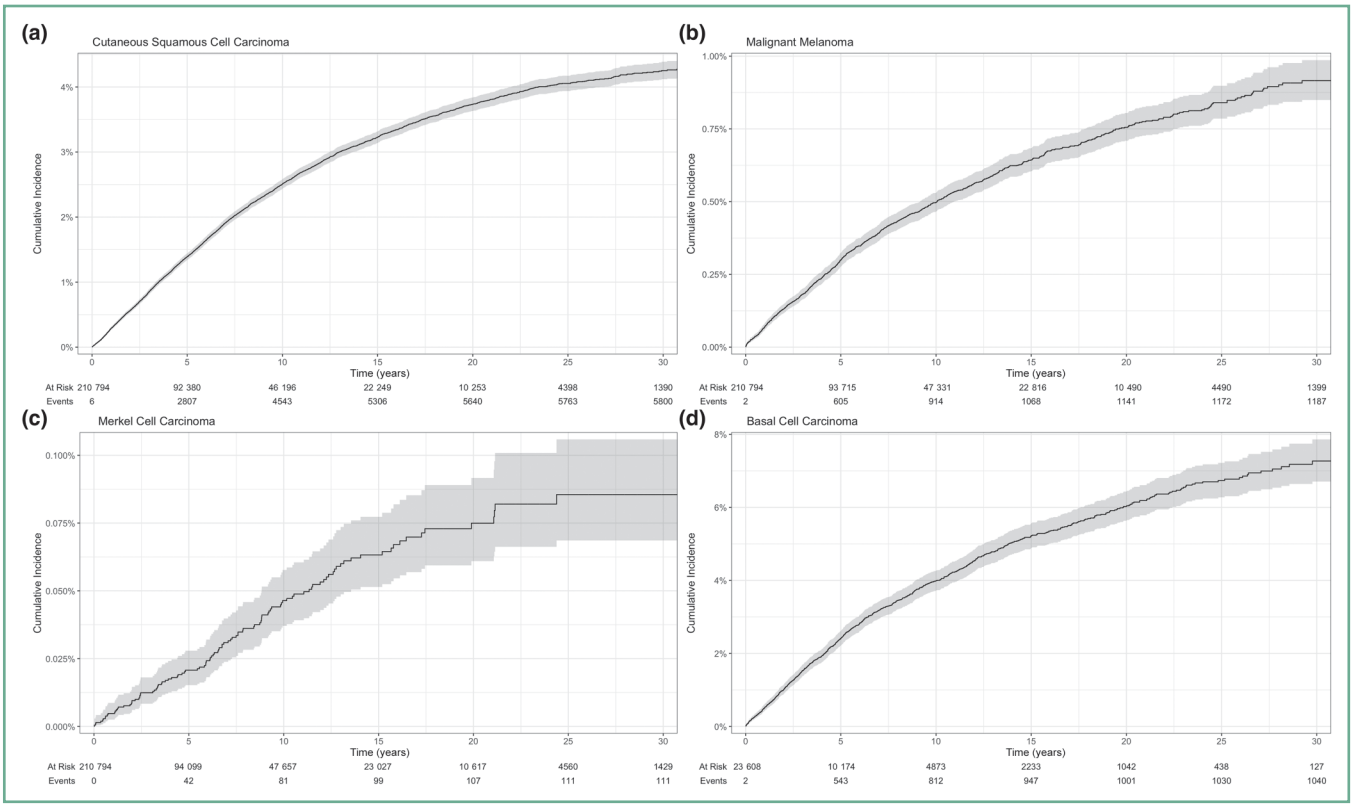

Figure 1 Cumulative incidence of developing (a) cutaneous squamous cell carcinoma, (b) malignant melanoma, (c) Merkel cell carcinoma and (d) basal cell carcinoma in patients with haematological malignancies over 31 years of follow-up.

subgroups, patients with CLL had a 10-year cumulative incidence of developing cSCC of 6%, which increased to 10% over 30 years (Figure S1, Table S5).

Relative and absolute excess risk compared with the general population

Patients with haematological malignancies had higher risks of skin cancer than the general population, with SIRs of 2.9 (95% CI 2.9–3.0) for cSCC, 1.8 (95% CI 1.7–1.9) for MM, 4.5 (95% CI 3.7–5.4) for MCC and 1.9 (95% CI 1.8–2.0) for BCC [Figure 2; Tables S9–S12 (see Supporting Information)]. BCC contributed most to the overall excess risk (AER 37.6/10 000 PY), followed by cSCC (AER 32.3/10 000 PY), MM (AER 4.4/10 000 PY) and MCC (AER 0.7/10 000 PY).

When stratified by haematological malignancy subgroup, SIRs and AERs for cSCC, MM and BCC were more than twofold higher for nearly all subgroups (Figure 2; Tables S9–S12). Due to the low incidence, SIRs for MCC varied widely between subgroups, ranging from 1.0 to 17.2. Again, patients with CLL had the highest risks for each of the four skin cancers, with SIRs of 4.4 (95% CI 4.2–4.6) for cSCC, 2.7 (95% CI 2.4–3.0) for MM, 9.3 (95% CI 7.0–12.5) for MCC and 2.6 (95% CI 2.3–2.9) for BCC (Figure 2; Tables S9–S12).

Stratified analyses

Sex

SIRs for each of the four skin cancers were significantly increased in both sexes but, for cSCC, were higher in men than in women [SIR 3.2 (95% CI 3.1–3.3) vs. SIR 2.5 (95% CI 2.4–2.7)] (Table 3). Also, AERs for men were more than twofold higher than in women (42.6 vs. 20.3 per 10 000 PY). A similar pattern was observed for BCC but not for MM or MCC (Table 3).

Among haematological malignancy subgroups, risks for each of the four skin cancers were generally comparable between the sexes, with the exception that men with CLL had higher SIRs for cSCC and BCC (Figures S5–S8, Tables S13–S16; see Supporting Information).

Age

Although the absolute risk of skin cancer increased with advancing age (peaking at 95.8 excess BCCs per 10 000 PY in men aged ≥ 75 years), the highest SIRs were seen in patients aged < 60 years across all skin cancers (Table 3).

Latency period

SIRs for each of the four skin cancers remained significantly increased across all latency periods, even 11–30 years after haematological malignancy diagnosis (Table 3). For cSCC and BCC, SIRs increased in the first 5 years after a haematological malignancy diagnosis, but – while remaining high and significantly elevated – showed a slight decrease thereafter. In contrast, SIRs for MM remained stable across different latency periods. AERs peaked during the latency period of 2–10 years (Table 3).

Primary treatment

No significant differences in SIRs or AERs were observed across different treatment modalities at diagnosis (no treatment, radiotherapy monotherapy, systemic treatment

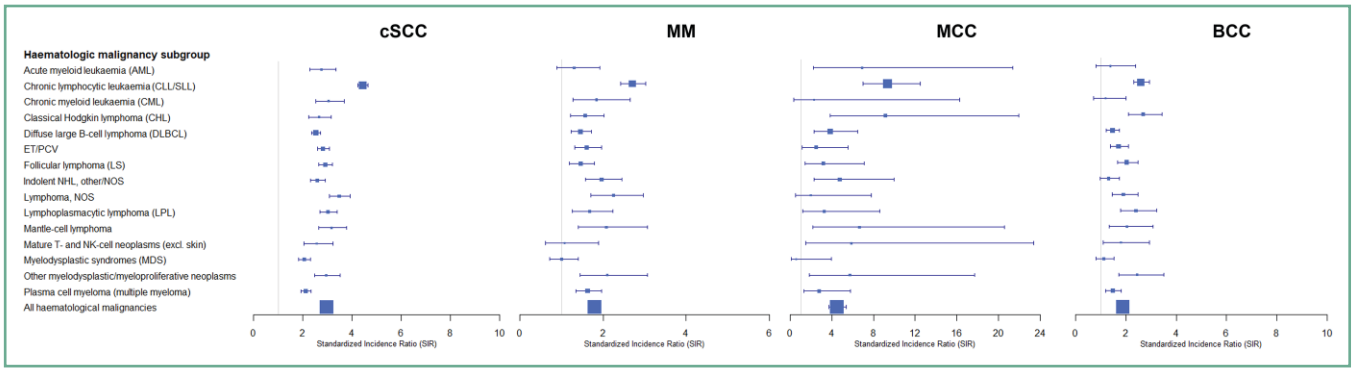

Figure 2 Risk of cutaneous squamous cell carcinoma (cSCC), malignant melanoma (MM), Merkel cell carcinoma (MCC) and basal cell carcinoma (BCC) in patients with haematological malignancies stratified by haematological malignancy subgroup. Different *x*-axis scale for MCC. ET, essential thrombocythaemia; NHL, non-Hodgkin lymphoma; NK, natural killer; NOS, not otherwise specified; PCV, polycythaemia vera.

monotherapy and HSCT), except for cSCC. Compared with the overall patient group (SIR 3.2, 95% CI 3.1–3.3), patients receiving radiotherapy monotherapy had a lower risk of developing cSCC (SIR 2.1, 95% CI 1.8–2.5), while those undergoing HSCT had a higher risk (SIR 5.4, 95% CI 4.5–6.4) (Table 3).

Discussion

We conducted a nationwide population-based study to investigate the risks of different types of skin cancer in > 200 000 patients with haematological malignancies over 31 years. We showed that patients with any type of haematological malignancy have markedly increased cumulative incidences of cSCC and BCC, as well as high relative and absolute risks of cSCC, MM, MCC and BCC. Compared with the general population, nearly all haematological malignancy subgroups showed a more than twofold increased risk of cSCC, BCC and MM. While the incidence of MCC was relatively low, SIRs were very high among different haematological malignancy subgroups, particularly in younger men. Elevated risks persisted for > 30 years after haematological malignancy diagnosis. Patients with CLL had the highest risks of all four skin cancers, including a more than ninefold increased risk of MCC, fivefold increased risk of cSCC, and a nearly threefold increased risk for MM and BCC compared with the general population.

Previous cancer registry studies from Denmark, Sweden and Switzerland reported a 5–8-fold increased risk of cSCC, a 3–4-fold increased risk of BCC and a 2–3-fold increased risk of MM in patients with NHL and CLL, respectively, compared with the general population.[19,20] Two studies investigated the incidence of MCC in patients with haematological malignancies using data from the Surveillance, Epidemiology, and End Results (SEER) registry.[21,22] They reported a threefold increased risk of NHL and a 7–8-fold increased risk of CLL. The SIRs found in our study in patients with CLL were similar for MM and BCC but somewhat lower for cSCC and higher for MCC. However, comparing SIRs between populations can be difficult because they strongly depend on underlying incidence rates.

The observed SIRs and AERs for cSCC and MM in our study are consistent with the findings of two Dutch studies that used data from the same population to investigate the risk of second primary malignancies in patients with follicular lymphoma and CLL. However, these studies reported higher cumulative incidences for cSCC and MM in both groups. Brewer *et al.* also reported higher cumulative incidences of cSCC and BCC in patients with CLL.[10] These discrepancies are likely to result from different methods used for calculating cumulative incidence. These studies used the '1 minus Kaplan–Meier' survival method, which censors deceased patients instead of considering them as competing risks, leading to an overestimation of risk probabilities.[23] In our study, we used the cumulative incidence curves method, which accounts for death as a competing risk, resulting in lower but more accurate risk estimates.

The pathophysiology behind haematological malignancy-associated skin cancer remains unclear, but several causative factors have been considered, including immunosuppression related to the haematological malignancy itself, the use of immunosuppressive medications, such as ciclosporin and azathioprine, ultraviolet (UV) exposure, and direct mutagenic effects of chemotherapy and radiotherapy.[1,7] Additionally, the increased incidence could be partly attributed to the heightened level of surveillance and diagnosis caused by regular follow-up visits in this patient population.

The observed increased skin cancer incidences in patients who were immunosuppressed for various reasons suggests that immune dysfunction accelerates the development of skin cancers after haematological malignancy, either independently or modulated by UV exposure, which is the most important environmental factor for these skin cancers.[24–26] MCC is also highly correlated with the presence of the Merkel cell polyomavirus, which is present in up to 80% of all MCCs and likely to be influenced by a weakened immune system.[27,28]

Immune dysfunction in patients with haematological malignancies can be profound, particularly in CLL, as it involves humoral and cell-mediated immunity. These immune system deficiencies impair the tumour surveillance system and may therefore not only account for the increased incidence of skin cancers, but also explain the increased aggressive behaviour.[1,7,8,10,29] This hypothesis is supported by our finding that the median time between haematological malignancy diagnosis and the skin cancer diagnosis was long enough to potentially be induced by impaired

Table 3 Standardized incidence ratios (SIRs) and absolute excess risks [AERs; per 10 000 person-years (PY)] of primary cutaneous squamous cell carcinomas (cSCCs), malignant melanomas (MMs), Merkel cell carcinomas (MCCs) and basal cell carcinomas (BCCs) as a second primary malignancy in different age categories, follow-up periods and type of primary treatment in patients with haematological malignancies

		Men						Women					
		Observed no. of cases	Expected no. of cases	SIR	95% CI	PY at risk	AER	Observed no. of cases	Expected no. of cases	SIR	95% CI	PY at risk	AER
Primary cSCC as second primary malignancy after haematological malignancy diagnosis													
Total		3996	1251	3.2	3.1–3.3	643 771	42.6	1806	710	2.5	2.4–2.7	539 310	20.3
Age (years)	< 60	208	38	5.5	4.8–6.3	242 856	7.0	89	26	3.4	2.7–4.1	179 697	3.5
	60–74	1618	403	4.0	3.8–4.2	258 942	46.9	620	210	3.0	2.7–3.2	198 533	20.7
	≥ 75	2170	810	2.7	2.6–2.8	141 972	95.8	1097	474	2.3	2.2–2.5	161 081	38.7
Follow-up (years)	0–1	826	327	2.5	2.4–2.7	179 395	27.8	359	157	2.3	2.1–2.5	140 992	14.3
	2–5	1468	414	3.5	3.4–3.7	215 646	48.9	602	224	2.7	2.5–2.9	178 315	21.2
	6–10	1028	277	3.7	3.5–3.9	137 427	54.6	478	172	2.8	2.5–3.0	120 854	25.3
	11–30	674	233	2.9	2.7–3.1	111 303	39.6	367	157	2.3	2.1–2.6	99 149	21.2
Treatment	No treatment	1947	618	3.1	3.0–3.3	237 337	56.0	858	335	2.6	2.4–2.7	203 374	25.7
	RT alone	149	70	2.1	1.8–2.5	46 464	17.0	90	45	2.0	1.6–2.5	39 587	11.5
	ST alone	1764	538	3.3	3.1–3.4	322 614	38.0	804	317	2.5	2.4–2.7	270 500	18.0
	HSCT	136	25	5.4	4.5–6.4	37 356	29.6	54	14	3.9	3.0–5.0	25 849	15.5
Primary MM as second primary malignancy after haematological malignancy diagnosis													
Total		711	386	1.8	1.7–2.0	655 008	5.0	476	276	1.7	1.6–1.9	543 453	3.7
Age (years)	< 60	134	69	1.9	1.6–2.3	242 904	2.7	103	66	1.6	1.3–1.9	179 362	2.1
	60–74	319	177	1.8	1.6–2.0	263 023	5.4	193	113	1.7	1.5–2.0	199 647	4.0
	≥ 75	258	140	1.8	1.6–2.1	149 081	7.9	180	98	1.8	1.6–2.1	164 444	5.0
Follow-up (years)	0–1	173	96	1.8	1.5–2.1	179 944	4.3	104	65	1.6	1.3–1.9	141 200	2.8
	2–5	251	126	2.0	1.8–2.3	218 767	5.7	161	88	1.8	1.6–2.1	179 524	4.0
	6–10	154	87	1.8	1.5–2.1	141 416	4.7	117	65	1.8	1.5–2.2	122 316	4.3
	11–30	133	77	1.7	1.5–2.1	114 880	4.9	94	58	1.6	1.3–2.0	100 413	3.6
Treatment	No treatment	335	167	2.0	1.8–2.2	242 858	6.9	205	112	1.8	1.6–2.1	205 534	4.5
	RT alone	52	23	2.2	1.7–2.9	46 816	6.2	33	18	1.8	1.3–2.5	39 743	3.7
	ST alone	301	177	1.7	1.5–1.9	327 601	3.8	213	133	1.6	1.4–1.8	272 261	2.9
	HSCT	23	18	1.3	0.8–1.9	37 733	1.3	25	13	2.0	1.4–3.0	25 915	4.8
Primary MCC as second primary malignancy after haematological malignancy diagnosis													
Total		63	13	4.8	3.7–6.1	657 829	0.8	48	11	4.2	3.1–5.5	545 806	0.7
Age (years)	< 60	5	0	14.1	5.9–33.8	243 485	0.2	0	0	0.0	0–inf.	179 975	0.0
	60–74	27	4	7.0	4.8–10.2	264 255	0.9	17	3	5.8	3.6–9.3	200 578	0.7
	≥ 75	31	9	3.4	2.4–4.9	150 089	1.5	31	8	3.7	2.6–5.3	165 252	1.4
Follow-up (years)	0–1	11	3	3.4	1.9–6.1	180 100	0.4	9	3	3.5	1.8–6.7	141 295	0.5
	2–5	11	4	2.5	1.4–4.6	219 513	0.3	17	4	4.6	2.9–7.5	179 985	0.7
	6–10	25	3	8.1	5.5–12.0	142 239	1.5	11	3	3.9	2.2–7.1	123 050	0.7
	11–30	16	3	6.1	3.7–10.0	115 977	1.2	11	2	4.5	2.5–8.1	101 476	0.8
Treatment	No treatment	27	7	4.0	2.8–5.9	244 093	0.8	25	6	4.5	3.0–6.6	206 440	0.9
	RT alone	1	1	1.4	0.2–9.8	47 047	0.1	1	1	1.3	0.2–9.5	39 922	0.1
	ST alone	33	6	5.9	4.2–8.3	328 870	0.8	22	5	4.4	2.9–6.7	273 387	0.6
	HSCT	2	0	8.0	2.0–31.8	37 818	0.5	0	0	0.0	0–inf.	26 057	–0.1
Primary BCC as second primary malignancy after haematological malignancy diagnosis													
Total		652	297	2.2	2.0–2.4	70 825	50.1	388	265	1.5	1.3–1.6	57 480	21.3
Age (years)	< 60	75	31	2.4	1.9–3.1	26 834	16.5	56	27	2.1	1.6–2.7	19 161	15.1
	60–74	302	136	2.2	2.0–2.5	28 961	57.3	167	89	1.9	1.6–2.2	21 808	35.6
	≥ 75	275	130	2.1	1.9–2.4	15 030	96.4	165	149	1.1	1.0–1.3	16 511	9.6
Follow-up (years)	0–1	153	84	1.8	1.6–2.1	20 489	33.6	85	67	1.3	1.0–1.6	15 630	11.3
	2–5	235	102	2.3	2.0–2.6	24 157	55.3	152	89	1.7	1.5–2.0	19 410	32.7
	6–10	142	63	2.3	1.9–2.7	14 716	53.7	76	61	1.3	1.0–1.6	12 605	12.3
	11–30	122	48	2.5	2.1–3.0	11 463	64.5	75	49	1.5	1.2–1.9	9835	26.5
Treatment	No treatment	321	137	2.3	2.1–2.6	26 294	70.0	173	122	1.4	1.2–1.6	22 299	22.7
	RT alone	42	20	2.1	1.5–2.8	5705	38.5	45	20	2.3	1.7–3.1	4796	52.8
	ST alone	273	132	2.1	1.8–2.3	35 891	39.3	160	119	1.3	1.2–1.6	28 602	14.3
	HSCT	16	8	2.0	1.2–3.3	2936	27.4	10	4	2.2	1.2–4.2	1782	31.1

CI, confidence interval; HSCT, haematological stem cell transplantation; RT, radiotherapy; ST, systemic therapy.

immune surveillance and the effects of chemotherapy and radiotherapy.

SIRs and AERs for cSCC and BCC were higher in men than in women, particularly in patients with CLL. These sex differences align with observations in the general population, where men generally have higher rates of cSCC and BCC.[30,31] This disparity may be explained by a biologic interaction of immune dysfunction associated with the haematological malignancy and higher cumulative UV exposure in men, often linked to occupational or behavioural factors.[32]

SIRs for all four skin cancers remained elevated across all latency periods, including 11–30 years after a haematological malignancy diagnosis. These findings highlight the need for long-term follow-up to capture the impact of impaired immune surveillance, UV exposure and treatment on skin cancer development.

The pattern of skin cancer development varied across latency periods and skin cancer types, with cSCC and BCC peaking in the first 5 years after diagnosis. While risks for MM also remained elevated, they did not significantly

increase over time. These differences in relative risk may reflect how UV exposure differentially affects these cancers and how the cumulative/ongoing effect of immunosuppression particularly affects the risk of cSCC and BCC.

Our study found that patients who received HSCT as first-line treatment for their haematological malignancy had a higher risk of developing cSCC, but not MM or BCC, compared with the overall patient group. This increased risk might be partly due to the occurrence of chronic graft-versus-host disease (GvHD) in HSCT recipients. GvHD affects about 50% of HSCT recipients.[33] Chronic GvHD often requires long-term immunosuppressive treatment, including azathioprine and ciclosporin, drugs known to increase photosensitivity to UVA and to contribute to the development of skin cancer, in particular cSCC.[34] Recent research has shown that azathioprine leaves a specific molecular fingerprint in skin cancers, further implicating it in the development of cSCC.[35]

The strengths of our large population-based study include the use of comprehensive and virtually complete data from a well-established nationwide cancer registry with 31 years of follow-up. These data allowed us to calculate robust risk estimates for multiple skin cancer types across patients with a haematological malignancy and stratify them by haematological malignancy subgroups, age, sex, duration of follow-up and primary treatment. This study therefore presents the most detailed data and represents one of the largest cohorts currently available to investigate the risks of multiple skin cancer types, including MCC, in patients with haematological malignancies.

Nevertheless, several limitations need to be considered. Firstly, all BCC analyses were conducted at the regional population level rather than nationwide. Despite this restriction, the regional cohort with > 23 000 patients showed no differences in baseline characteristics from the nationwide cohort. Therefore, we believe our BCC findings are equally representative. Secondly, the NCR collects only information on primary treatments administered within the first year of haematological malignancy diagnosis. Subsequent treatments, including additional chemotherapeutics, targeted therapies or prolonged immunosuppression, are not captured, potentially underestimating their cumulative long-term effect on skin cancer risks. Future research should investigate the effects of baseline and subsequent treatments to better understand their impact on skin cancer development.

In conclusion, this nationwide population-based study found that patients with all types of haematological malignancies, and particularly CLL, are at increased risk of developing different types of skin cancer for at least 30 years. Patients and physicians should be educated about the high and lifelong risk of skin cancer in this patient population, also with regard to less common but highly aggressive cancers such as MCC. Sun-protective measures should be strongly recommended, along with instructions on how to recognize the different types of skin cancer and on how to perform regular skin self-examinations.

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Conflicts of interest

M.W. has received honoraria for lectures and advisory board meetings from Sanofi, Regeneron and Sun Pharma. T.N. is a section editor for the *BJD*. The other authors declare no conflicts of interest.

Data availability

The data presented in this study were provided by the Netherlands Cancer Registry (NCR) to the Erasmus MC Institute and are therefore not publicly available. However, these data are available upon reasonable request from the corresponding author and with permission of the NCR.

Ethics statement

According to the Central Committee on Research involving Human Subjects, this observational, noninterventional study did not require approval from an ethics committee. The Privacy Review Board and the Scientific Committee of the Netherlands Cancer Registry approved the use of anonymous data for this study.

Patient consent

Not applicable.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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