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Cancer type and histology influence cutaneous immunotherapy toxicities: a multi-institutional cohort study

Guihong Wan,[1,2] Sara Khattab,[1] Bonnie W. Leung,[1,3,4] Shijia Zhang,[1] Nga Nguyen,[1] Matthew Tran,[1] Chuck Lin,[1] Crystal Chang,[1] Nora Alexander,[1] Ruple Jairath,[1] Jordan Phillipps,[1] Kimberly Tang,[1] Ahmad Rajeh,[1] Leyre Zubiri,[1] Steven T. Chen,[1] Shadmehr Demehri,[1] Kun-Hsing Yu,[2] Alexander Gusev,[4] Shawn G. Kwatra,[5] Nicole R. LeBoeuf,[2,3,4] Kerry L. Reynolds[1,2] and Yevgeniy R. Semenov[1,2]

[1]Department of Dermatology, Massachusetts General Hospital, Boston, MA
[2]Harvard Medical School, Boston, MA
[3]Department of Dermatology, Brigham and Women's Hospital, Boston, MA
[4]Center for Cutaneous Oncology, Department of Dermatology, Dana-Farber Cancer Institute, Boston, MA
[5]Department of Dermatology, Johns Hopkins University, Baltimore, MD, USA

Correspondence: Yevgeniy R. Semenov. Email: ysemenov@mgh.harvard.edu

G.W., S.K. and B.W.L. contributed equally to this work.

K.L.R. and Y.R.S. are co-senior authors.

Lay summary

Cutaneous immune-related adverse events (cirAEs) are the most common complications to occur for oncology patients treated with immune checkpoint inhibitors (ICIs). cirAEs can lead to increased use of healthcare resources and significant morbidity. Identifying patients who are at increased risk of developing cirAEs may improve quality of life and outcomes.

In this study, we aimed to investigate the influence of cancer organ system and histology on the development of cirAEs and survival outcomes. To do this, we included a cohort of patients retrospectively between 1 December 2011 and 30 October 2020. We identified 3668 ICI recipients who were seen at Massachusetts General Brigham and Dana-Farber in Boston, Massachusetts. Of these, 669 people developed cirAEs. Multivariate Cox proportional hazards models were used to investigate the impact of cancer organ system and histology on cirAE development, after adjusting for demographics, Charlson Comorbidity Index, ICI type, cancer stage at ICI start, and year of ICI initiation. Time-varying Cox proportional hazards modelling was used to examine the impact of cirAE development on mortality.

We found that, compared with other nonepithelial cancers, patients with cutaneous squamous cell carcinoma (cSCC) and melanoma were at significantly higher risk of cirAEs. The increased risk of cirAEs translated into an adjusted survival benefit for melanoma and cSCC. This study improves our understanding of patients who are at highest risk of developing cirAEs – those with melanoma and cSCC. Therefore, many patients could benefit from appropriate counselling and close monitoring by their oncologists and dermatologists throughout ICI therapy.

Linked Article: Ribero *et al. Br J Dermatol* 2024; **191**:12–13.

Abstract

Background Cutaneous immune-related adverse events (cirAEs) are the most common toxicities to occur in the setting of immune checkpoint inhibitor (ICI) therapy. Identifying patients who are at increased risk of developing cirAEs may improve quality of life and outcomes.

Objectives To investigate the influence of cancer type and histology on the development of cirAEs in the setting of ICI therapy and survival outcomes.

Methods This retrospective cohort study included patients recruited between 1 December 2011 and 30 October 2020. They received ICI from 2011 to 2020 with follow-up of outcomes through October 2021. We identified 3668 recipients of ICI therapy who were seen at Massachusetts General Brigham and Dana-Farber. Of these, 669 developed cirAEs. Records that were incomplete or categories of insufficient sample size were excluded from the study cohort. Multivariate Cox proportional hazards models were used to investigate the impact of cancer organ system and histology on cirAE development, after adjusting for demographics, Charlson Comorbidity Index, ICI type, cancer stage at ICI initiation, and year of ICI initiation. Time-varying Cox proportional hazards modelling was used to examine the impact of cirAE development on mortality.

Results Compared with other nonepithelial cancers (neuroendocrine, leukaemia, lymphoma, myeloma, sarcoma and central nervous system malignancies), cutaneous squamous cell carcinoma [cSCC; hazard ratio (HR) 3.57, $P<0.001$], melanoma (HR 2.09, $P<0.001$), head and neck adenocarcinoma (HR 2.13, $P=0.009$), genitourinary transitional cell carcinoma (HR 2.15, $P<0.001$) and genitourinary adenocarcinoma (HR 1.53, $P=0.037$) were at significantly higher risk of cirAEs in multivariate analyses. The increased risk of cirAEs translated into an adjusted survival benefit for melanoma (HR 0.37, $P<0.001$) and cSCC (HR 0.51, $P=0.011$).

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Conclusions The highest rate of cirAEs and subsequent survival benefits were observed in cutaneous malignancies treated with ICI therapies. This study improves our understanding of patients who are at highest risk of developing cirAEs and would, therefore, benefit from appropriate counselling and closer monitoring by their oncologists and dermatologists throughout their ICI therapy. Limitations include its retrospective nature and cohort from one geography.

What is already known about this topic?

- Cutaneous immune-related adverse events (cirAEs) are the most common toxicities to occur in the setting of immune checkpoint inhibitor (ICI) therapy.
- Identifying patients who are at increased risk of developing cirAEs may improve quality of life and outcomes.

What does this study add?

- In this retrospective cohort study, cutaneous malignancies, including squamous cell carcinoma and melanoma, are associated with increased risk of cirAEs and subsequent survival benefits.
- Given their increased risk, patients with cutaneous malignancies may benefit from appropriate counselling and monitoring during ICI therapy.

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of a rapidly growing number of advanced malignancies. ICIs have been approved by the US Food and Drug Administration for the treatment of metastatic melanoma, nonsmall cell lung cancer, renal cell carcinoma, cutaneous squamous cell carcinoma (cSCC), urothelial carcinoma, breast cancer and others.[1] The percentage of patients with cancer who are eligible for ICI treatment has grown from 1.54% in 2011 to 36.1% in 2019.[2,3] This tremendous growth in interest and promise of ICIs highlights the importance of understanding their benefits and adverse effects. In fact, immune-related adverse events (irAEs) have been reported to occur in up to half of those receiving ICIs, of which cutaneous irAEs (cirAEs) are the most common.[4,5] These toxicities are associated with significant morbidity and mortality, but their mechanisms are not well understood. Several studies have identified associations between shared germline genetic predispositions.[6,7] Multiple investigations have suggested epitope spreading, the diversification of epitope specificity from the initial focused immune response, as a potential mechanism that may explain toxicities such as vitiligo occurring in the setting of melanoma treatment.[8,9] Recent observations of prognostically favourable outcomes from nonvitiligo cirAEs (which comprise the majority of cirAEs) suggest that there are other mechanisms mediating improved therapeutic response among ICI recipients.[10,11] Additionally, emerging evidence suggests a greater incidence of cirAEs among patients with melanoma.[12,13] Our group has previously investigated various risk factors for the development of cirAEs, but the influence of cancer histology type on cirAE development has not yet been investigated.[14–16] Cancer histology type may play an important role in the pathogenesis of cirAEs as well as their downstream implications on ICI outcomes; however, large-scale evidence on this relationship is limited. To address this knowledge gap, we performed a multi-institutional cohort study to explore the relationship between cancer organ system and histology, cirAE incidence and ICI outcomes.

Patients and methods

Study cohort collection

After institutional review board approval (protocol # 2020P002307), patients with cancer receiving ICI treatment from Massachusetts General Brigham Healthcare System (MGB) and Dana-Farber Cancer Institute between 1 December 2011 and 30 October 2020 were selected as the study cohort. We enrolled patients with cancer who had received ICIs from 2011 to 2020 with follow-up of outcomes through October 2021. Records that were incomplete or of insufficient sample size (e.g. adenosquamous cancer histological type or patients identifying as Native Hawaiian or Alaska Native demographically) were excluded from the study cohort. A study design flowchart is shown in Figure 1.

Data extraction

Relevant variables from patient records were extracted from the MGB Research Patient Data Registry[17] and the Enterprise Data Warehouse. Extracted features include age, sex, race/ethnicity, ICI type, dermatology visits, date of ICI initiation, date of cirAE, date of death or last follow-up, and International Classification of Diseases codes used to calculate the Charlson Comorbidity Index (CCI) score at ICI initiation. ICIs included anti-PD-1 (programmed cell death protein 1: pembrolizumab, nivolumab, cemiplimab), anti-PD-L1 (programmed death ligand 1: atezolizumab, avelumab, durvalumab), anti-CTLA-4 (cytotoxic T-lymphocyte-associated protein 4: ipilimumab), and combination therapy (CTLA-4 and either PD-1 or PD-L1 inhibitor).

Chart review

To ascertain cirAE status, a manual chart review was conducted by two trained independent research analysts (B.W.L. and N.N.) using a standardized method (additional details are provided in Methods S1; see Supporting Information) with

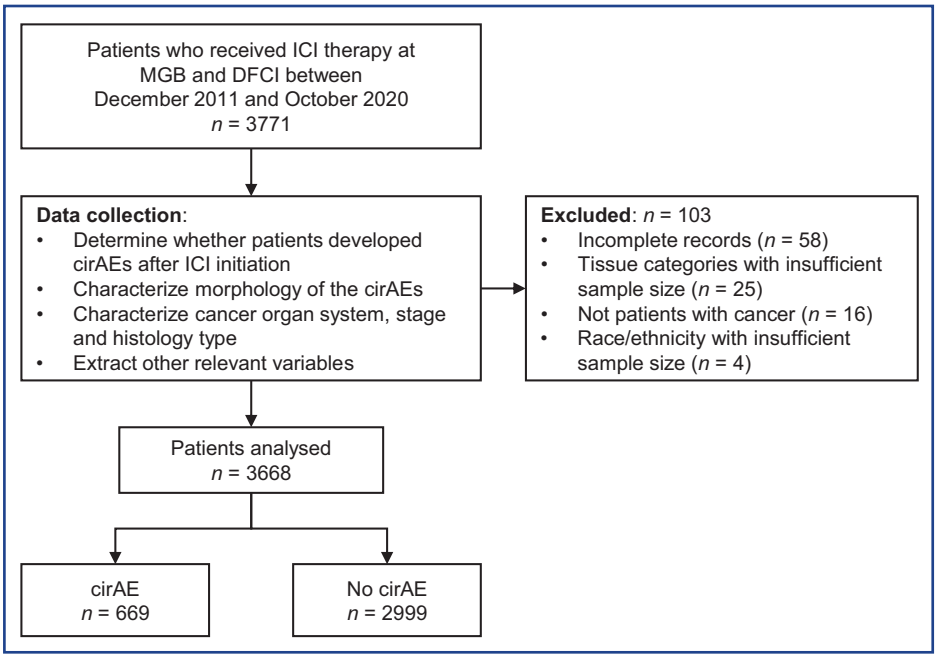

Figure 1 Study design flowchart. cirAE, cutaneous immune-related adverse event; DFCI, Dana-Farber Cancer Institute; ICI, immune checkpoint inhibitor; MGB, Massachusetts General Brigham Healthcare System.

arbitration of discordant cases by a third reviewer (Y.R.S., board-certified dermatologist with expertise in immunotherapy toxicities). cirAE definitions were based on Common Terminology Criteria for Adverse Events version 5.0.[18] For each patient who developed cutaneous involvement after immunotherapy, a likelihood score was assigned from 1 (highly unlikely) to 4 (highly likely). The likelihood score is based on eruption timing, morphology, absence of competing risk factors, and histological confirmation, when available. Patients with likelihood scores of 3 or 4 were identified as having cirAEs. Furthermore, we reviewed patients' charts for cancer stage, cancer organ system, histopathological characteristics, photographs and eruption morphologies, when available, which are consistent with those documented in existing literature.[10] Cancers were grouped by cancer organ system [skin, gastrointestinal (GI), gynaecological (GYN), genitourinary (GU), head and neck, thoracic] and histological subtype: epithelial (adenoid, squamous, transitional) and nonepithelial (melanoma and other nonepithelial) (Table S1; see Supporting Information). The 'other nonepithelial' category includes neuroendocrine tumours, leukaemia, lymphoma, myeloma, sarcoma and central nervous system malignancies. An interaction term was created between these two variables for our primary models. Cancer staging was extracted based on the American Joint Committee on Cancer (AJCC) 8th edition manual.[19] Cancers that are not classified by traditional AJCC staging were combined into an 'Other Staging Criteria' category. This category included certain central nervous system malignancies (such as glioblastomas and meningiomas), haematological malignancies (such as Hodgkin lymphoma and multiple myeloma) and anorectal mucosal melanomas.

Statistical analysis

To compare the variables between cirAE and non-cirAE groups, we used Pearson's χ^2 test for categorical variables and the *t*-test for continuous variables. Kaplan–Meier curves were used to compare the likelihood of developing cirAEs stratified by cancer organ system and histology type. Multivariate Cox proportional hazards modelling was used to investigate the relationship between the interaction term (cancer organ system and histology type) and cirAE development, after adjusting for age at ICI initiation, sex, CCI, ICI type, cancer stage at ICI start, and year of ICI initiation. To reduce contribution from guarantee-time bias, we used time-varying Cox proportional hazards models to examine the downstream impact of cirAE development on mortality, after adjusting for the interaction term between cancer organ system and histology type, age at ICI initiation, sex, CCI, ICI type, cancer stage at ICI start, and year of ICI initiation.

Results

We identified 3668 recipients of ICI seen at our combined institutions; 669 (18%) were found to have experienced cirAEs. The median duration of follow-up was 914 days for patients with cirAEs and 384 days for patients without cirAEs. Of these 669 patients with cirAEs, 38% had cutaneous malignancies and 62% had noncutaneous malignancies. There were no significant differences in dermatological evaluations between cutaneous and noncutaneous malignancies among patients with cirAE (52% vs. 59%, $P=0.102$). Baseline characteristics are shown in Table 1 (with additional details in Table S2; see Supporting Information). In univariate analyses, cancer organ system and histology type were both significantly associated with cirAE development ($P<0.001$). In multivariate analyses, cirAEs were more likely to occur in patients with melanoma [hazard ratio (HR) 2.09, 95% confidence interval (CI) 1.56–2.80, $P<0.001$], transitional cell carcinoma (TCC) (HR 2.16, 95% CI 1.44–3.25, $P<0.001$) and,

Table 1 Baseline characteristics of the study population

	cirAE (*N*=669) *n* (%)	No cirAE (*N*=2999) *n* (%)	*P*-value
ICI type			
CTLA-4	21 (3.1)	63 (2.1)	< 0.001
PD-1	464 (69.4)	2301 (76.7)	
PD-L1	65 (9.7)	376 (12.5)	
Combination	119 (17.8)	259 (8.6)	
Cancer histology type			
Adenoid	234 (35.0)	1391 (46.4)	< 0.001
Squamous	85 (12.7)	429 (14.3)	
Transitional	41 (6.1)	132 (4.4)	
Melanoma[a]	236 (35.3)	527 (17.6)	
Other nonepithelial	73 (10.9)	520 (17.3)	
Cancer organ system			
GI	56 (8.4)	368 (12.3)	< 0.001
GU	84 (12.6)	288 (9.6)	
GYN	51 (7.6)	256 (8.5)	
Head and neck	60 (9.0)	231 (7.7)	
Skin	255 (38.1)	571 (19.0)	
Thoracic	122 (18.2)	957 (31.9)	
Other	41 (6.1)	328 (10.9)	
Tumour type[b]			
GI adenocarcinoma	53 (7.9)	335 (11.2)	< 0.001
GI SCC	1 (0.1)	23 (0.8)	
GU adenocarcinoma	42 (6.3)	149 (5.0)	
GU SCC	1 (0.1)	2 (0.1)	
GU transitional cell carcinoma	41 (6.1)	132 (4.4)	
GYN adenocarcinoma	47 (7.0)	235 (7.8)	
GYN SCC	2 (0.3)	14 (0.5)	
Head and neck adenocarcinoma	15 (2.2)	34 (1.1)	
Head and neck SCC	44 (6.6)	193 (6.4)	
Melanoma[a]	236 (35.3)	527 (17.6)	
Cutaneous SCC	12 (1.8)	19 (0.6)	
Thoracic adenocarcinoma	77 (11.5)	636 (21.2)	
Thoracic SCC	25 (3.7)	178 (5.9)	
Other nonepithelial	73 (10.9)	520 (17.3)	
Other adenocarcinoma	0 (0)	2 (0.1)	
Mortality			
Alive	333 (49.8)	1152 (38.4)	< 0.001
Dead	336 (50.2)	1847 (61.6)	

[a]Melanoma category: cutaneous, acral and mucosal melanomas. [b]Tumour type: the interaction term between cancer organ system and cancer histology type variables. We excluded the 'Other adenocarcinoma' type due to the small sample size. cirAE, cutaneous immune-related adverse event; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; GI, gastrointestinal; GU, genitourinary; GYN, gynaecological; ICI, immune checkpoint inhibitor; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; SCC, squamous cell carcinoma.

to a lesser extent, squamous cell carcinoma (SCC) (HR 1.42, 95% CI 1.01–1.98, $P=0.042$) (Figure 2 and Table S3; see Supporting Information). The distribution of cirAE morphology varied and was significantly different by cancer organ system and histology type ($P<0.001$) (Figure S1, Tables S4 and S5; see Supporting Information).

Compared with other nonepithelial cancers (sarcomas, haematological malignancies and central nervous system malignancies), cSCC (39%; HR 3.57; 95% CI 1.90–6.69, $P<0.001$), melanoma [31%, HR 2.09 (CI 1.56–2.80), $P<0.001$], GU TCC [24%, HR 2.15 (CI 1.43–3.23), $P<0.001$], head and neck adenocarcinoma [31%, HR 2.13 (CI 1.20–3.78), $P=0.009$], head and neck SCC [19%, HR 1.58 (CI 1.06–2.34), $P=0.024$] and GU adenocarcinoma [22%, HR 1.53 (CI 1.03–2.29), $P=0.037$] were at significantly higher risk of cirAE development in multivariate analyses (Table 2 with substages adjusted in Table S6; see Supporting Information). Table S7 (see Supporting Information) examines the independent impact of cancer organ system on cirAE development, which shows an increased risk of cirAEs in cutaneous, GU, and head and neck malignancies.

Furthermore, the increased risk of cirAEs translated into adjusted survival benefits in melanoma (HR 0.37, 95% CI 0.31–0.43, $P<0.001$), adenocarcinoma (HR 0.81, 95% CI 0.71–0.92, $P<0.001$) and SCC (HR 0.81, 95% CI 0.69–0.95, $P=0.009$) (Table S8; see Supporting Information). Specifically, adjusted improved survival was seen in the setting of cSCC (HR 0.51, 95% CI 0.30–0.86, $P=0.011$) in comparison with other nonepithelial cancers (Table 3 with additional details in Table S9 and with substages adjusted in Table S10; see Supporting Information). GU adenocarcinoma (HR 0.54, 95% CI 0.44–0.68, $P<0.001$) and head and neck adenocarcinoma (HR 0.45, 95% CI 0.29–0.68, $P<0.001$) appeared to have improved survival as well. Broadly, we observed subsequent survival benefits in cancers of the skin and GU system (Table S11; see Supporting Information). Landmark analyses at 3 and 6 months on associations of the interactive term between cirAE and cancer histology and

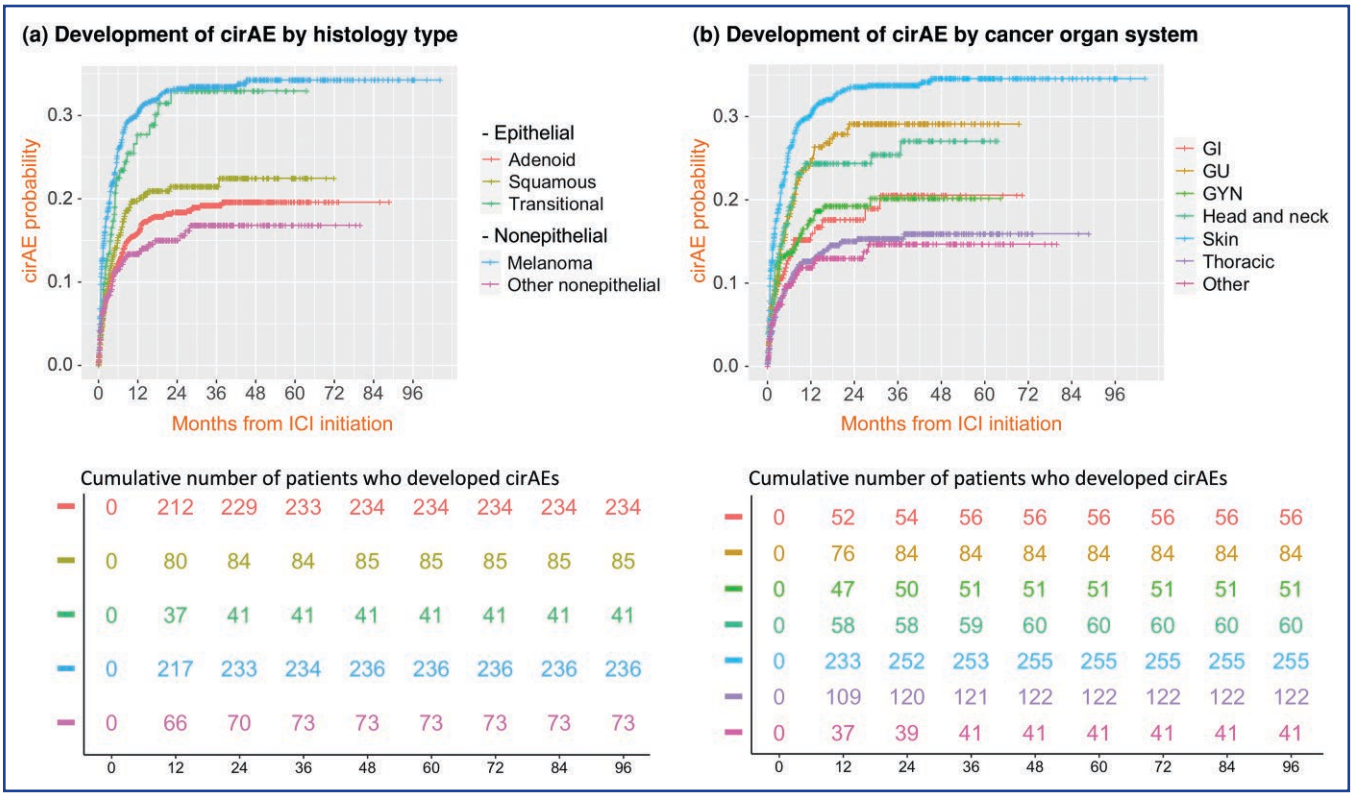

Figure 2 Probability of cirAE development by cancer histology type and cancer organ system. (a) The probability of developing cirAEs by histology type with cumulative number of patients who developed cirAEs by months from ICI initiation. (b) The probability of cirAE development by cancer organ system with cumulative number of patients who developed cirAEs by months from ICI initiation. cirAE, cutaneous immune-related adverse event; GI, gastrointestinal; GU, genitourinary; GYN, gynaecological; ICI, immune checkpoint inhibitor.

organ type with overall survival are detailed in Tables S12 and S13 (see Supporting Information).

Discussion

This is a large-scale study to investigate the influence of cancer histological type on the development of cirAEs and clinical outcomes. We leveraged a manually phenotyped cohort to granularly substratify cirAEs by cancer organ system and cancer histological type and demonstrated that cirAEs are preferentially observed among patients with cutaneous malignancies. Specifically, the incidence of cirAEs is highest among patients with cSCC (38.7% of patients with cSCC), followed closely by melanoma (30.9% of patients with melanoma). We observed that the prognostic impact of cirAEs was also most significant among patients with cutaneous malignancies (HR 0.51, 95% CI 0.30–0.86, $P=0.011$ for cSCC; HR 0.37, 95% CI 0.31–0.43, $P<0.001$ for melanoma). Lastly, elevated risks of cirAEs were also observed among patients with head and neck adenocarcinoma, GU TCC and GU adenocarcinoma.

These findings are consistent overall with a prior study showing that cirAE development is a favourable clinical indicator that is associated with improved response to ICI therapy and patient survival.[10] Furthermore, our findings confirm prior population-level observations based on insurance claims data, which found increased risk of cirAEs among patients with melanoma and renal cell carcinoma.[12] In addition, consistent with prior studies, we found an association between melanoma and vitiligo, which gives further evidence for the phenomenon of epitope spreading, as there are likely to be analogous melanocyte-lineage antigens shared by normal melanocytes and melanocytes in melanoma.[9] In epitope spreading, immune responses against primary epitopes spread to other distinct epitopes in the same tissue type.[9,20–22] As ICIs reactivate the immune system to target neoplastic melanocytes, the shared antigens between neoplastic and normal melanocytes also lead to the destruction of normal melanocytes, resulting in vitiligo.[9]

While epitope spreading helps to explain the association between vitiligo and melanoma, vitiligo accounts for only 7.2% of cirAEs in the melanoma population, and we observed survival benefits among both vitiliginous and nonvitiliginous morphologies of cirAEs. Therefore, we hypothesize that a separate biologic mechanism may explain this relationship beyond epitope spreading alone. Specifically, the highest observed rates of cirAEs seen among patients with cutaneous malignancies may be explained by a tissue-homing process. Dendritic cells recognizing tumour antigens in melanoma and cSCC may travel to secondary lymphoid organs to activate naïve T cells to differentiate into effector T cells and facilitate their homing back to the skin, the original tissue of activation, where these T cells drive a more generalized inflammatory response against the tumour and surrounding tissue, resulting in the development of cirAEs.[23]

Existing literature has postulated that the migration of immune cells that are skin- and tumour-specific plays an important role in the host immune response. Studies have

Table 2 Association of interaction term between cancer organ system and histology type with development of cirAEs using a multivariate Cox proportional hazard model

Characteristic	HR	95% CI	*P*-value
Tumour type[a]			
Other nonepithelial	[Reference]	[Reference]	
GI adenocarcinoma	1.14	0.78–1.66	0.5
GI SCC	0.34	0.05–2.44	0.3
GU adenocarcinoma	1.53	1.03–2.29	0.037
GU SCC	3.63	0.49–26.8	0.2
GU transitional cell carcinoma	2.15	1.43–3.23	< 0.001
GYN adenocarcinoma	1.31	0.88–1.95	0.2
GYN SCC	1.04	0.25–4.28	> 0.9
Head and neck adenocarcinoma	2.13	1.20–3.78	0.009
Head and neck SCC	1.58	1.06–2.34	0.024
Melanoma[b]	2.09	1.56–2.80	< 0.001
Cutaneous SCC	3.57	1.90–6.69	< 0.001
Thoracic adenocarcinoma	0.87	0.62–1.23	0.4
Thoracic SCC	1.04	0.65–1.67	0.9
Race/Ethnicity			
White	[Reference]	[Reference]	
Asian	1.39	0.93–2.09	0.11
Black or African American	0.60	0.30–1.22	0.2
Hispanic or Latino	0.59	0.15–2.37	0.5
Unknown	0.47	0.22–0.99	0.047
Sex			
Female	[Reference]	[Reference]	
Male	1.03	0.87–1.22	0.7
Year of ICI start	1.05	0.99–1.12	0.13
Charlson comorbidity index	0.97	0.93–1.02	0.3
Age at ICI start	1.00	1.00–1.01	0.5
ICI type			
CTLA-4	[Reference]	[Reference]	
PD-1	0.88	0.56–1.39	0.6
PD-L1	0.77	0.46–1.30	0.3
Combination	1.69	1.05–2.74	0.031
Cancer stage at ICI start[c]			
IV	[Reference]	[Reference]	
I or II	1.11	0.87–1.41	0.4
III	0.78	0.60–1.01	0.061
Other staging criteria	1.02	0.60–1.74	> 0.9

CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; GI, gastrointestinal; GU, genitourinary; GYN, gynaecological; HR, hazard ratio; ICI, immune checkpoint inhibitor; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; SCC, squamous cell carcinoma. [a]Tumour type: the interaction term between cancer organ system and cancer histology type variables. [b]Melanoma category: cutaneous, acral and mucosal melanomas. [c]Stages I, II, III and IV are based on the American Joint Committee on Cancer staging system; other staging criteria include cancer types that are described using different means of classification, such as certain neurological cancers (glioblastoma, meningioma, central nervous system lymphoma), haematological malignancies (such as Hodgkin lymphoma, non-Hodgkin lymphoma and multiple myeloma), which use alternative staging conventions, and anorectal melanomas, which are also described using an alternative staging system.

found tumour-infiltrating lymphocytes to be a significant positive pathological prognostic factor.[24–26] Immune cell homing is a complex process that is mediated by numerous cell types and homing receptors. Analogously, a prior study found a correlation between nonsmall cell lung cancer and respiratory irAEs, which suggests that irAEs may be driven by an immune response to the specific characteristics of the primary tumour and further underscores a tissue-homing process.[27] Likewise, the increased risk of cirAEs among patients with SCC (mostly driven by cSCC, and, to a lesser extent, SCC of the head and neck) may suggest similarities that underlie their disease biology.

These findings identify clinical populations that are at increased risk for cirAE development, as well as situations in which these toxicities may be prognostically favourable. Both observations are of significant clinical benefit, enabling healthcare providers to enhance surveillance efforts among patients at greatest risk for cirAEs, as well as facilitating patient counselling in explaining the prognostic significance of these toxicities in a more precise, cancer-driven approach.[28] For example, this may support referral to dermatology earlier and at the initiation of ICIs for patients who are at highest risk of developing cirAEs, i.e. the patients with cutaneous malignancies. This may lead to improved quality of life and better utilization of healthcare resources.[29,30] As a result, these observations add to the growing body of literature on cirAEs and lay the foundation for an increasingly personalized approach to cirAE surveillance, management and implications for downstream outcomes. Moreover, our observations suggest possible mechanisms for the development of these toxicities and their observed differential impact on immunotherapy response among different cancers.

Table 3 Association of interaction term between cancer organ system and histology type with overall survival using a multivariate time-varying Cox proportional hazard model

Characteristic[a]	HR	95% CI	*P*-value
cirAE	0.88	0.78–1.0	0.041
Tumour type[b]			
Other nonepithelial	[Reference]	[Reference]	
GI adenocarcinoma	1.20	1.03–1.41	0.023
GI SCC	1.01	0.60–1.69	> 0.9
GU adenocarcinoma	0.54	0.44–0.68	< 0.001
GU SCC	0.56	0.08–4.05	0.6
GU transitional cell carcinoma	0.79	0.63–0.99	0.037
GYN adenocarcinoma	0.75	0.62–0.90	0.003
GYN SCC	0.86	0.46–1.62	0.6
Head and neck adenocarcinoma	0.45	0.29–0.68	< 0.001
Head and neck SCC	0.81	0.66–0.99	0.041
Melanoma[c]	0.37	0.31–0.43	< 0.001
Cutaneous SCC	0.51	0.30–0.86	0.011
Thoracic adenocarcinoma	0.79	0.68–0.91	0.001
Thoracic SCC	0.85	0.70–1.05	0.13
Cancer stage at ICI start			
IV	[Reference]	[Reference]	
I or II	0.56	0.28–1.12	0.10
III	0.66	0.57–0.76	< 0.001
Other staging criteria	0.71	0.55–0.92	0.010

CCI, Charlson Comorbidity Index; CI, confidence interval; cirAE, cutaneous immune-related adverse events; GI, gastrointestinal; GU, genitourinary; GYN, gynaecological; HR, hazard ratio; ICI, immune checkpoint inhibitor; SCC, squamous cell carcinoma. [a]The model was adjusted by sex, race/ethnicity, CCI, age at ICI start, cancer stage at ICI start, ICI type, and year of ICI start. The full model is presented in Table S9. [b]Interaction term between cancer organ system and cancer histology type variables. [c]Melanoma category: cutaneous, acral, and mucosal melanomas.

Limitations of this study include its retrospective nature and use of predominantly White patients from a single geography. However, the included multi-institutional cohort represents one of the largest, deeply phenotyped populations of ICI recipients in the USA. In addition, there may be variability between clinicians who documented the patient presentations and the interpretations by researchers who completed the chart review. To mitigate this concern, cirAE status was ascertained by two independent trained research analysts (B.W.L. and N.N.). Cases that did not meet concordance were further evaluated by a board-certified dermatologist with expertise in immunotherapy toxicities (Y.R.S.).

While shared antigenicity helps explain the success of antitumour response in the setting of melanoma and vitiligo, higher incidence of cirAEs and improved survival in cutaneous malignancies, both melanoma and cSCC, demonstrate that tissue-homing, a more global process that illustrates organotrophic selectivity,[23] may contribute as well. This study improves our understanding of patients who are at highest risk of developing cirAEs and would, therefore, benefit from appropriate counselling and closer monitoring by their oncologists and dermatologists throughout their ICI therapy. Further studies are needed to directly investigate the underlying immunopathogenesis of cirAEs proposed in this study and the implications of toxicity management on survival.

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Conflicts of interest

S.G.K. is an advisory board member/consultant for AbbVie, Celldex Therapeutics, Galderma, Incyte Corporation, Johnson & Johnson, Kiniksa Pharmaceuticals, Novartis Pharmaceuticals Corporation, Pfizer, Regeneron Pharmaceuticals and Sanofi, and has served as an investigator for Galderma, Kiniksa Pharmaceuticals, Pfizer Inc. and Sanofi. N.R.L. is a consultant and has received honoraria from Bayer, Sanofi, Seattle Genetics, Silverback and Synox Therapeutics outside the submitted work. Y.R.S. is an

advisory board member/consultant and has received honoraria from Castle Biosciences, Galderma, Incyte Corporation and Sanofi outside the submitted work.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics statement

This study was reviewed and approved by Massachusetts General Brigham Institutional Review Boards; protocol # 2020P002307.

Supporting Information

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

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