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Declining incidence of keratinocyte carcinoma in organ transplant recipients*

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Summary

Background All organ transplant populations are predisposed to increased rates of keratinocyte carcinoma (KC). Since this increased risk was first appreciated, immunosuppressive regimens have changed and organ transplant recipients (OTRs) have been aggressively screened for KC. There is a perception that these measures have impacted on KC incidence but there is a paucity of population-based studies on post-transplant rates of basal cell carcinoma (BCC).

Objectives To identify trends in incidence rates for KC following solid organ transplantation over the past two decades.

Methods This nationwide, population-based study included all solid OTRs transplanted between 1994 and 2014. Patient data were matched to national cancer registry data to determine the standardized incidence ratio (SIR) of KC in solid OTRs compared with the general population.

Results In total 3580 solid OTRs were included. The total follow-up time was 28 407 person-years (median follow-up 7·11 years). The overall SIRs for squamous cell carcinoma (SCC) and BCC were 19·7 and 7·0, respectively. Our study documents a progressive fall in the SIRs for SCC and BCC from peak SIRs (95% confidence intervals) in 1994–1996 of 26·4 (21·5–32·4) and 9·1 (7·4–11·3) to 6·3 (2·3–16·7) and 3·2 (1·4–7·1) in 2012–2014, respectively. The ratio of SCC to BCC has remained at 3 to 1 over the last two decades.

Conclusions Our study is the first to demonstrate a significant reduction over the past two decades in the incidences of both SCC and BCC following solid organ transplantation. The SCC-to-BCC ratio was maintained, demonstrating that both are reducing equally. This trend coincided with temporal changes in immunosuppressive protocols and the introduction of skin cancer prevention programmes.

What's already known about this topic?

- Prior studies have shown that the risk of cutaneous squamous cell carcinoma (SCC) has declined over recent decades following solid organ transplantation.
- It is not known whether the risk of basal cell carcinoma (BCC) has reduced in line with this.

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Conflicts of interest
None to declare.

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What does this study add?

- Our study documents a progressive fall in the risk of SCC and BCC following solid organ transplantation over the last two decades.
- The SCC-to-BCC ratio was maintained, demonstrating that both are reducing equally.
- The trends observed in our study coincided with temporal changes in immunosuppressive protocols and the introduction of cancer prevention programmes, suggesting that these factors have positively impacted on the risk of keratinocyte carcinoma in this cohort.

Organ transplantation saves lives and improves quality of life in patients affected by end organ failure; however many transplant recipients develop multiple and aggressive keratinocyte carcinomas (KCs), with significant morbidity and mortality.[1] Population incidence rates of KC continue to rise, as recently reported for Ireland.[2] The cumulative incidence of KC also increases for individual organ transplant recipients with duration post-transplantation.[3] Conversely, despite increasing mean age at transplantation and improved survival post-transplantation,[4–6] the evidence does not support a rise in the rate of KC in recent decades.[7–9] Recent studies have shown both a reduction and no change in the incidence of KC in the current transplantation era. This era has seen a phasing out of traditional ciclosporin- and azathioprine-based immunosuppressive regimens, therapeutic dosing that reduces the overall immunosuppressive burden, and more focused primary and secondary skin cancer prevention programmes.

Interpreting incidence rates over time requires allowance for variables impacting on skin cancer risk including sex, the ageing profile of organ transplant recipients, variable patient ethnicity and skin type, and the changes in immunosuppressive protocols and dosing for different organ transplant recipients.[10] The time to first skin cancer post-transplant averages close to 10 years,[3] so a lag phase can pre-date the emergence of obvious incidence trends. The majority of national cancer registries are restricted to documenting squamous cell carcinoma (SCC) only.[7,9] There is an absence of population-based studies examining the incidence and trends of post-transplant basal cell carcinoma (BCC).[11] Our aim was to identify trends in incidence rates for both SCC and BCC following renal, liver, heart and lung transplantation over the past two decades and to examine variables that contribute to these trends.

Patients and methods

Study population

Since 1994, the National Cancer Registry Ireland (NCRI) has registered all histologically confirmed first SCCs and first BCCs for the largely homogeneous Republic of Ireland population. Renal, heart, liver and lung transplant services commenced in Ireland in 1964, 1985, 1993 and 2005, respectively. Following solid organ transplantation, all transplant recipients are enrolled in an organ-specific database. For this study, a data processing agreement between the individual transplant centres and the NCRI was obtained, along with ethical approval from the institutional review boards. We combined datasets from the Irish national transplant centres for renal, heart, liver and lung transplantation and matched them with NCRI data from 1 January 1994 to 31 December 2014. Only patients transplanted after 1 January 1994 were included in our analysis. We excluded patients with a history of skin cancer prior to transplantation.

The follow-up period was used as a proxy of duration of immunosuppression and was calculated from the date of transplantation to the date of first SCC or BCC diagnosis, death or end of the study period (31 December 2014), whichever came first. We grouped patients by 3-year time periods of transplantation and in blocks of 5-year follow-up periods post-transplantation.

Individual patient immunosuppressive protocols were not available for data analysis; however, organ-specific protocols are consistent throughout Ireland, as outlined in Figure 1. Immunosuppression following renal transplantation included azathioprine, ciclosporin and prednisolone prior to 1996. Between 1996 and 2003, azathioprine and ciclosporin were gradually replaced by mycophenolate mofetil and tacrolimus, with a complete transition taking place from 2003. Induction immunosuppression with antithymocyte globulin was used in high-immunological-risk renal transplants, accounting for $< 10\%$ of transplants performed. Basiliximab in addition to corticosteroids has been the mainstay induction regimen used for kidney transplantation since circa 2004. Protocols following lung and heart transplantation included azathioprine, ciclosporin and prednisolone prior to 2010. After 2010, azathioprine and ciclosporin were replaced by mycophenolate mofetil and tacrolimus. Induction immunosuppression for lung and heart transplantation includes basiliximab at days 0 and 4 for all patients transplanted after 2004 and occasionally intravenous human immunoglobulin for those deemed at high immunological risk.

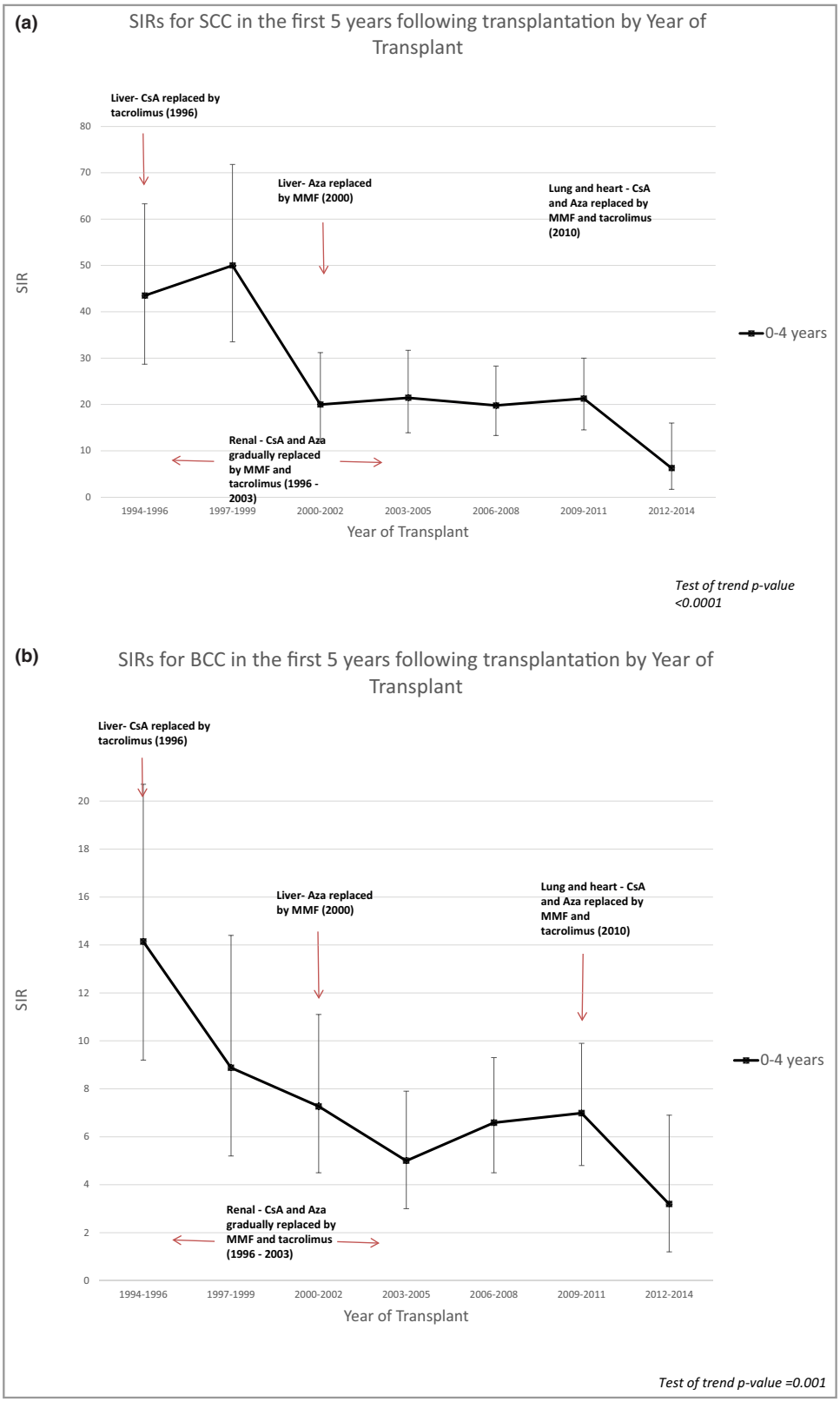

Fig 1. Standardized incidence ratios (SIRs) for keratinocyte cancers in the first 5 years following transplantation by year of transplant. (a) Squamous cell carcinoma, (b) basal cell carcinoma. CsA, ciclosporin; Aza, azathioprine; MMF, mycophenolate mofetil.

Protocols following liver transplantation included azathioprine, ciclosporin and prednisolone prior to 1996. After 1996, ciclosporin was replaced by tacrolimus, and after 2000, azathioprine was replaced by mycophenolate mofetil. Current immunosuppressive protocols following liver transplantation include a minimum of prednisolone and tacrolimus for 3 months, with addition of mycophenolate mofetil for graft rejection. No induction immunosuppression has been used in liver transplantation since programme inception in 1993.

Statistical analysis

Standardized incidence ratios (SIRs) were calculated by dividing the observed number of cases over the expected number of cases. Observed cases included all first SCC (invasive tumours only) and first BCC, occurring in the transplant cohort, during the study period. Expected cases were calculated based on matched (age-, sex- and year-specific) incidence rates for the general Irish population and the number of person-years at risk.

To compare time to first skin cancer between population subgroups, we used an independent-samples *t*-test (sex and skin cancer type) and ANOVA (age at transplantation and transplant type). A test of trend was calculated by taking the observed and expected incidence (SIR) across time periods and generating a P-value for the trend over time.

Multivariate Poisson regression analysis was carried out to evaluate covariates impacting on the SIRs for SCC and BCC (separately) in organ transplant recipients. Covariates included sex, age at transplantation, year of transplant, follow-up period (i.e. time from transplantation) and organ transplant type. SIRs were calculated relative to the general population for each of the crossed categories of these covariates, and the Poisson regression model was fitted with observed cases as the outcome and expected cases included as an offset. Univariate analysis of predictors was conducted to obtain unadjusted SIRs followed by multivariate modelling where all predictors were included in the same Poisson regression model to obtain incident rate ratios. The incident rate ratios were calculated using year of transplant as a categorical variable. The test-of-trend P-values quoted in the multivariate regression model were calculated using year of transplant as a continuous variable. Stata 15 was the software package used for all statistical analysis (StataCorp, College Station, TX, U.S.A.).

Results

Patient demographics

In total, 3580 patients who received a solid organ transplant between 1 January 1994 and 31 December 2014 were included in our analysis; 2446 (68%) were renal transplant recipients, with 726 (20%) liver, 216 (6%) heart and 192 (5%) lung (Table 1). We excluded 83 patients with a history of KC prior to transplantation. The annual number of transplant recipients has increased over time from 140 in 1994 to 192 in 2014. The total follow-up time was 28 407 person-years, with renal transplant recipients making up the largest cohort (20 835 person-years). The median follow-up time was 7·1 years, with longer follow-up post-transplant in the heart (8·8 years) and renal (7·7 years) compared with the liver (5·7 years) and lung (4·0 years) cohorts.

The sex distribution demonstrates a male preponderance (63%) across all organ transplant recipients, most markedly in the heart transplant population, where almost four out of five recipients were male. The average age at transplantation was 44·8 years (range 1–77), and it was greater for liver and heart transplant recipients (49·9 and 47·2 years, respectively) than for renal and lung transplant recipients (43·3 and 41·2 years, respectively). A higher proportion of lung transplant recipients were under 30 years old at the time of transplantation compared with other organ transplant recipients (36% vs. 9–22%). The distribution of renal transplant recipients was relatively balanced across age groups. The distribution of transplant recipients across year of transplant varied by solid organ transplant type, as outlined in Table 1. There was a twofold greater representation of patients with longer follow-up post-transplant (> 10 years) in the renal (38%) and heart (44%) cohorts compared with lung (19%) and liver (22%).

Time to first skin cancer

The average time to first SCC or BCC was 6·3 years (range 0·03–20·4). There was no difference in time to first SCC compared with time to first BCC (7 vs. 6·4 years, respectively; $P = 0·2$). There was no statistically significant difference in time to first skin cancer in terms of sex ($P = 0·12$) or solid organ transplant type ($P = 0·19$). Time to first skin cancer was longer in those transplanted at a younger age ($P < 0·001$).

Squamous cell carcinoma risk

There were 359 first SCCs diagnosed in our transplant cohort between 1994 and 2014 [overall SIR 19·7, 95% confidence interval (CI) 17·7–21·8]. In the 0–4-year follow-up period, the SIR fell by > 50% in those transplanted after 1999 compared with those transplanted before 1999 (test of trend $P < 0·001$; Fig. 1a). The SIR then remained stable in those transplanted up to 2011 but fell further to 6·3 in those transplanted during 2012–2014, likely due to it being the end of the study period (Table S1; see Supporting Information). A similar trend was observed in the 5–9-year follow-up cohort, where the SIR for SCC reduced from 58 (1994–1996) to 16 (2006–2008).

Multivariate Poisson regression analysis shows that in our transplant cohort, male sex did not confer any additional risk of SCC compared with that observed in the general population ($P = 0·45$; Table 2).

Younger patients had a higher SIR than older patients ($P < 0·001$), likely due to the rarity of SCC in the young immunocompetent population. The test of trend showed that the SIR for SCC was lower for those transplanted in more recent years

Table 1 Demographic details for all solid organ transplant recipients

	Total	Renal	Heart	Lung	Liver
Number	3580	2446	216	192	726
Follow-up time (person-years)	28 407	20 835	1900	1030	4642
Follow-up time (years)					
Median	7·11	7·71	8·81	3·96	5·69
Mean ± SD	7·93 ± 5·7	8·52 ± 5·73	8·79 ± 6·2	5·37 ± 4·88	6·39 ± 5·12
Male	2256 (63)	1536 (63)	167 (77)	116 (60)	437 (60)
Female	1324 (37)	910 (37)	49 (23)	76 (40)	289 (40)
Age at transplant (years)					
Average (range)	44·8 (1–77)	43·3 (1–77)	47·2 (1–70)	41·2 (10–72)	49·9 (16–72)
< 30	702 (20)	531 (22)	35 (16)	69 (36)	67 (9)
30–39	560 (16)	445 (18)	17 (8)	28 (15)	70 (10)
40–49	714 (20)	493 (20)	40 (19)	21 (11)	160 (22)
50–59	916 (26)	534 (22)	86 (40)	38 (20)	258 (36)
≥ 60	688 (19)	443 (18)	38 (18)	36 (19)	171 (24)
Year of transplant					
1994–1996	410 (12)	310 (13)	47 (22)	6 (3)	47 (7)
1997–1999	393 (11)	293 (12)	38 (18)	5 (3)	57 (8)
2000–2002	488 (14)	324 (13)	41 (19)	27 (14)	96 (13)
2003–2005	509 (14)	334 (14)	34 (16)	29 (15)	112 (15)
2006–2008	585 (16)	368 (15)	24 (11)	34 (18)	159 (22)
2009–2011	583 (16)	410 (17)	17 (8)	21 (11)	135 (19)
2012–2014	612 (17)	407 (17)	15 (7)	70 (37)	120 (17)
Follow-up time (years)					
0–4	1330 (37)	824 (34)	68 (32)	111 (58)	327 (45)
5–9	1017 (28)	680 (28)	54 (25)	45 (23)	238 (33)
10–14	708 (20)	518 (21)	52 (24)	27 (14)	111 (15)
15–19	460 (13)	375 (15)	36 (17)	9 (5)	40 (6)
≥ 20	65 (2)	49 (2)	6 (3)	0 (0)	10 (1)

Data are presented as n (%) unless stated otherwise.

($P \leq 0{\cdot}001$). While the unadjusted SIRs increased with duration of follow-up (from 16·1 in the first 5 years to 24·9 in those followed up for 15–19 years), once factors including year of transplant and age are accounted for, the incidence of first SCC relative to the general population is actually estimated to decrease with duration of follow-up, reflecting that most transplant recipients who develop a first KC will do so within the first 10 years.

As discussed in our methodology, subsequent KC was not included in our analysis, and this is therefore not reflective of the burden of multiple KCs as time from transplantation increases. The SIR was approximately 40% lower for liver vs. renal transplant recipients ($P = 0{\cdot}003$). The SIR was approximately 50% higher following lung vs. renal transplantation; however, this did not reach statistical significance, likely due to the limited sample size. There was no statistically significant difference in the SIR for heart vs. renal transplant recipients.

Basal cell carcinoma risk

There were 362 first BCCs diagnosed in our transplant cohort over the 20-year study period, giving an overall SIR of 7·0, 95% CI 6·3–7·8. In the 0–4-year follow-up period, the SIR for BCC gradually fell as the year of transplant increased, with the greatest fall noted after 1996 ($P = 0{\cdot}001$; Fig. 1b). The SIR for BCC also declined in the 5–9-year follow-up period, from 16 (1994–1996) to 6 (2006–2008) (Table S2; see Supporting Information).

Multivariate Poisson regression analysis shows that the SIR for BCC is estimated to be 26% lower for female vs. male transplant recipients ($P = 0{\cdot}01$; Table 3). Those aged > 50 years at the time of transplantation had a significantly lower SIR for BCC than those aged < 30 years at the time of transplantation, reflecting the relative rarity of BCC in the young immunocompetent population. The test of trend showed that the SIR for BCC was lower for those transplanted in more recent years ($P = 0{\cdot}02$). The SIR for BCC was lower for liver vs. renal transplant recipients ($P = 0{\cdot}004$). The SIR for BCC was higher in lung and heart transplant recipients than in renal transplant recipients; however, this did not reach statistical significance ($P = 0{\cdot}45$ and $P = 0{\cdot}43$, respectively).

Ratio of squamous cell carcinoma to basal cell carcinoma

The overall ratio of SCC to BCC following solid organ transplantation was 2·8 : 1 (95% CI 2·4–3·2). The ratio appears to be relatively stable across year of transplant, evidenced by the overlapping CIs ($P > 0{\cdot}05$; Table S3; see Supporting

Table 2 Univariate and multivariate regression analysis for squamous cell carcinoma

					Univariate analysis				Multivariate analysis			Likelihood ratio test[a]
	Patient numbers	Person-years	Observed	Expected	Unadjusted SIR	IRR	95% CI	P-value	IRR	95% CI	P-value	P-value
Sex												0·45
Male	2256	17 760	291	14·4	20·16	1	–	–	1	–	–	
Female	1324	10 647	68	3·7	18·55	0·92	0·71–1·20	0·54	0·89	0·68–1·16	0·40	
Year of transplant												< 0·001
1994–1996	410	5890	90	3·4	26·38	1	–	–	1	–	–	
1997–1999	393	5283	70	3·1	22·75	0·86	0·63–1·18	0·35	0·92	0·66–1·27	0·60	
2000–2002	488	5278	66	3·5	18·91	0·72	0·52–0·98	0·040	0·51	0·34–0·75	0·001	
2003–2005	509	4627	51	3·3	15·30	0·58	0·41–0·82	0·002	0·42	0·27–0·63	< 0·001	
2006–2008	585	3972	44	2·6	17·14	0·65	0·45–0·93	0·019	0·40	0·25–0·64	< 0·001	
2009–2011	583	2445	34	1·6	21·51	0·82	0·55–1·21	0·31	0·55	0·32–0·93	0·026	
2012–2014	612	912	4	0·6	6·26	0·24	0·09–0·65	0·005	0·17	0·05–0·51	0·002	
Age at transplant (years)												< 0·001
< 30	702	6691	13	0·1	175·9	1	–	–	1	–	–	
30–39	560	5018	27	0·4	74·18	0·42	0·22–0·82	0·011	0·42	0·21–0·81	0·010	
40–49	714	6090	66	1·7	38·93	0·22	0·12–0·40	< 0·001	0·21	0·12–0·39	< 0·001	
50–59	916	6704	124	6·0	20·50	0·12	0·07–0·21	< 0·001	0·11	0·06–0·20	< 0·001	
≥ 60	688	3904	129	9·9	13·01	0·07	0·04–0·13	< 0·001	0·06	0·04–0·12	< 0·001	
Transplant type												0·01
Renal	2446	20 835	269	12·4	21·72	1	–	–	1	–	–	
Heart	216	1899	36	1·9	19·20	0·88	0·62–1·25	0·49	0·94	0·66–1·35	0·75	
Lung	192	1030	11	0·3	31·61	1·46	0·80–2·66	0·22	1·47	0·79–2·71	0·22	
Liver	726	4642	43	3·5	12·31	0·57	0·41–0·78	0·001	0·61	0·44–0·85	0·003	
Follow-up time (years)												< 0·001
0–4	1330	2883	33	2·0	16·11	1	–	–	1	–	–	
5–9	1017	7516	110	5·5	20·05	1·24	0·84–1·84	0·27	1·09	0·68–1·76	0·72	
10–14	708	8721	109	5·6	19·51	1·21	0·82–1·79	0·34	0·77	0·45–1·30	0·32	
15–19	460	7952	92	4·4	21·02	1·30	0·88–1·94	0·19	0·37	0·21–0·65	0·001	
≥ 20	65	1334	15	0·6	24·90	1·55	0·84–2·85	0·16	0·34	0·16–0·73	0·006	

SIR, standardized incidence ratio; IRR, incidence rate ratio; CI, confidence interval. Variables adjusted for include sex, year of transplant, age at transplant, transplant type and follow-up time. [a]Likelihood ratio test P-values were calculated using the continuous version of year of transplant (test of trend). IRR was calculated using the categorical version of year of transplant.

Information). A similar ratio of SCC to BCC was seen across different solid organ transplant recipients, including renal (2·8 : 1, 95% CI 2·4–3·4), lung (3·5 : 1, 95% CI 1·4–9·0) and liver (2·9 : 1, 95% CI 1·8–4·4). The ratio was slightly diminished for heart transplant recipients (2·2 : 1, 95% CI 1·4–3·5).

Discussion

All organ transplant populations are predisposed to increased KC rates and increased morbidity and mortality relative to the nontransplant population.[1] This study is the first to examine data on all KC subtypes for all solid organ transplant recipients across two decades, allowing for a lag phase that takes into account the effect of changes in immunosuppressive protocols. With over 28 000 person-years of follow-up and a median duration of follow-up of over 7 years, we have demonstrated a significant reduction over this period in the incidence of both SCC and BCC following solid organ transplantation. This is in contrast to population incidence figures for KC increasing since early 2000 and despite increased duration of survival post-transplantation for all organ transplant recipients.[2]

The reducing incidence of KC observed in our study was consistent across different follow-up times, pointing to a sustained and continuing reduction in SIR since the early 1990s. Our findings mirror the reduced risk of cutaneous SCC observed in other studies.[7,8] Prior studies included an era comparison showing that the risk of cutaneous SCC has declined over the last 30 years following solid organ transplantation in Norway.[7] Similarly, a Dutch study found that the risk of cutaneous SCC decreased over the last 20 years in their renal transplant cohort.[8] In contrast, a Swedish study reported no statistically significant difference in the rate of cutaneous SCC following solid organ transplantation over the last 30 years; however, in that study the year of transplant was grouped by decade, which may have concealed subtle changes in the incidence of KC over shorter time periods.[9]

The average time to first skin cancer was 6·3 years, which is shorter than that previously documented in the literature (8–18·3 years),[3,11–13] potentially due to older age at

Table 3 Univariate and multivariate regression analysis for basal cell carcinoma

					Univariate analysis				Multivariate analysis			Likelihood ratio test[a]
	Patient numbers	Person -years	Observed	Expected	Unadjusted SIR	IRR	95% CI	P-value	IRR	95% CI	P-value	P-value
Sex												0·01
Male	2256	17 760	267	34·8	7·67	1	–	–	1	–	–	
Female	1324	10 647	95	16·3	5·82	0·76	0·60–0·96	0·020	0·74	0·58–0·94	0·014	
Year of transplant												0·02
1994–1996	410	5890	84	9·2	9·14	1	–	–	1	–	–	
1997–1999	393	5283	63	8·7	7·26	0·79	0·57–1·10	0·17	0·85	0·60–1·20	0·35	
2000–2002	488	5278	75	9·9	7·55	0·83	0·61–1·13	0·23	0·70	0·45–1·06	0·094	
2003–2005	509	4627	52	9·0	5·77	0·63	0·45–0·89	0·009	0·54	0·35–0·85	0·007	
2006–2008	585	3972	48	7·6	6·28	0·69	0·48–0·98	0·038	0·61	0·37–1·01	0·054	
2009–2011	583	2445	34	4·8	7·10	0·78	0·52–1·16	0·21	0·71	0·40–1·26	0·24	
2012–2014	612	912	6	1·9	3·19	0·35	0·15–0·80	0·013	0·32	0·12–0·88	0·026	
Age at transplant (years)												< 0·001
< 30	702	6691	15	0·9	16·78	1	–	–	1	–	–	
30–39	560	5018	32	2·9	11·18	0·67	0·36–1·23	0·19	0·67	0·36–1·25	0·21	
40–49	714	6090	82	8·1	10·07	0·60	0·35–1·04	0·069	0·60	0·35–1·05	0·075	
50–59	916	6704	122	18·7	6·52	0·39	0·23–0·66	0·001	0·39	0·23–0·68	0·001	
≥ 60	688	3904	111	20·5	5·41	0·32	0·19–0·55	< 0·001	0·32	0·18–0·55	< 0·001	
Transplant type												0·01
Renal	2446	20 835	265	34·7	7·64	1	–	–	1	–	–	
Heart	216	1899	40	4·6	8·75	1·14	0·82–1·60	0·43	1·15	0·82–1·61	0·43	
Lung	192	1030	11	1·2	8·96	1·17	0·64–2·14	0·61	1·26	0·69–2·33	0·45	
Liver	726	4642	46	10·7	4·32	0·56	0·41–0·77	< 0·001	0·63	0·45–0·86	0·004	
Follow-up time (years)												0·24
0–4	1330	2883	34	6·0	5·68	1	–	–	1	–	–	
5–9	1017	7516	100	15·2	6·59	1·16	0·79–1·71	0·46	1·04	0·63–1·72	0·87	
10–14	708	8721	120	16·1	7·46	1·31	0·90–1·92	0·16	1·00	0·57–1·76	1·00	
15–19	460	7952	92	12·2	7·54	1·33	0·90–1·97	0·16	0·65	0·35–1·20	0·17	
≥ 20	65	1334	16	1·7	9·47	1·67	0·92–3·02	0·092	0·67	0·31–1·48	0·32	

SIR, standardized incidence ratio; IRR, incidence rate ratio; CI, confidence interval. Variables adjusted for include sex, year of transplant, age at transplant, transplant type and follow-up time. [a]Likelihood ratio test P-values were calculated using the continuous version of year of transplant (test of trend). IRR was calculated using the categorical version of year of transplant.

transplantation, more aggressive skin cancer screening and a higher proportion of patients with fair skin type in the Irish population. Not surprisingly, time to first skin cancer was shorter in older vs. younger transplant recipients, reflecting the importance of stratifying older patients and those with significant actinic change for early screening immediate post-transplant. Our research group had previously demonstrated that in renal transplant patients aged > 50 years there was a significant increase in skin cancer rates from as early as 2 years post-transplant.[11] Sex and skin cancer subtype did not impact on time to first skin cancer, and neither did organ transplant type, suggesting that similar approaches to screening and prevention could be promoted across all solid organ transplant programmes.

The sex distribution for SCC was similar in the transplant population and the general population, as opposed to BCC, where male sex conferred an additional risk for BCC compared with that observed in the general population. We know there are innate differences in the pathogenesis of SCC and BCC and also in the sex-induced immunosuppression caused by ultraviolet radiation, which might explain this difference.[14] The SIRs for BCC and SCC were significantly higher for renal vs. liver transplant recipients, potentially due to shorter mean follow-up and lower burden of immunosuppression. There was no statistically significant differences in the SIRs for SCC or BCC between heart or lung and renal transplant recipients. Younger patients had higher SIRs for SCC and BCC than older patients, reflecting how skin cancer is strongly age dependent and the relative rarity of KC in the young immunocompetent population.

The ratio of BCC to SCC is approximately 3 : 1 in the general population, with some geographical variability.[11,15,16] Reversal of this ratio has been demonstrated in the immunosuppressed population, although national incidence figures in many countries are restricted to documenting first skin cancer and SCC only.[17,18] Our study documents a fall in the risk of BCC following solid organ transplantation over the last two decades that consistently parallels the fall in SCC incidence, maintaining the 3 : 1 incidence ratio (SCC : BCC), the inverse of that seen in the general population. This consistent

reduction across skin tumour type and organ transplant type supports the concept that general measures such as changing immunosuppressive protocols and overall decreased immunosuppressive burden, along with primary and secondary skin cancer prevention, may have impacted on the incidence of KC in this high-risk cohort.

Renal transplant recipients had a far greater representation in the overall data (six times more than heart and lung combined), a fact that must be considered when interpreting the overall trend of declining skin cancer rates. However, the overall analysis of SIRs by organ transplant type did show comparable patterns across each of the transplant recipient groups. Our group had previously speculated on how transplant-associated KC may be impacting on worldwide increases in skin cancer incidence.[11] The incidence of skin cancer has increased in Ireland since the early 2000s. This in turn may exaggerate the fall in SIR of KC due to an increase in the expected number of cases of skin cancer.[2] While there was an approximate 10% increase in the rate of skin cancer in the general Irish population between 2000 and 2005, we saw a much greater reduction in the SIR for SCC (around 50%). Furthermore, the greatest fall in SIR for BCC occurred prior to 2000, therefore the reduction in SIR observed in this study cannot be explained solely by the rising rate of skin cancer in the general population.[2]

This study examined incidence rates of first KC to illustrate trends over time, as only first SCC and first BCC are recorded in detail by the NCRI. The standard practice of cancer registries not to document all subsequent skin cancers fully tends to underestimate the overall disease burden in organ transplant recipients, who often develop multiple KCs. Additional limitations include lack of data on patient skin type and details of immunosuppressive agents used.

Our data confirm a halving of the risk of KC, for both SCC and BCC, since the turn of the century. We have also shown that the ratio of SCC to BCC is stable over time, supporting our finding that the risks of SCC and BCC are reducing equally. Despite these promising results, our study does not account for second or subsequent skin cancers, and the risk of KC remains significantly higher in organ transplant recipients than in the general population, highlighting that skin cancer remains an important problem in organ transplant recipients. Our data do not definitively allow us to differentiate the root cause for this reduced incidence. However, it is likely that a combination of factors has contributed: changes in immunosuppressive protocols and dosing providing adequate immunosuppression without the same level of carcinogenicity;[19–22] the results of aggressive screening for and management of precancerous skin lesions with topical, destructive and chemopreventive treatments; and targeted education timed to motivate a population to self-examine their skin and protect it from the sun.[23–27]

The addition of skin cancer end points should be mandatory for all future studies evaluating newer immunosuppressive regimens. As patients survive longer post-transplant it is important that primary and secondary preventive measures are continually emphasized in this high-risk cohort.

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Supporting Information

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

Table S1 Standardized incidence ratios (confidence intervals) for squamous cell carcinoma based on year of transplant and follow-up period.

Table S2 Standardized incidence ratios (confidence intervals) for basal cell carcinoma based on year of transplant and follow-up period.

Table S3 Ratio of squamous cell carcinoma to basal cell carcinoma (standardized incidence ratios) by year of transplant and follow-up.