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A population-based study of skin cancer incidence and prevalence in renal transplant recipients

F.J. Moloney, H. Comber,* P. O'Lorcain,* P. O'Kelly,† P.J. Conlon† and G.M. Murphy

Departments of Dermatology and †Nephrology, Beaumont Hospital, Dublin 9, Ireland
**National Cancer Registry, Cork, Ireland*

Summary

Background Cancers occurring following solid organ transplantation are a rapidly growing public health concern. Defining the extent of the problem has been limited by surveillance systems with incomplete registration of cases and the paucity of reliable national incidence data.

Objectives To determine the incidence of all cancers following renal transplantation and to make a detailed examination of trends and patterns associated with post-renal transplant skin cancers.

Methods Integration of data from the national renal transplant database and the national cancer registry in Ireland enabled accurate determination of the number of renal transplant recipients (RTRs) with skin cancers and other malignancies in the time period 1 January 1994 to 31 December 2001.

Results We demonstrated a biphasic increase in skin cancer incidence following renal transplantation, determined by the age at transplantation. There was a steady increase in risk for older RTRs (age 50+ years) from year 2 post-transplant, whereas the increased risk in younger RTRs (age < 50 years) occurred later but much more significantly, reaching 200 times the risk for an age-matched nontransplanted population by year 6 post-transplant. The number of nonmelanoma skin cancers (NMSCs) registered in RTRs accounted for 1% of all NMSCs registered nationally over the study period. The standardized incidence rates for invasive NMSC (33-fold increase) and *in situ* carcinoma of the skin (65-fold increase) were significantly increased ($P < 0{\cdot}05$). The risk for invasive squamous cell carcinoma (SCC) was increased 82-fold compared with the nontransplanted population. Male RTRs were at particular risk of invasive SCC at sun-exposed sites such as the scalp and the external ear. Risk of malignant melanoma and Kaposi sarcoma were also increased relative to the nontransplanted population.

Conclusions This comprehensive national study illustrates how rates of skin cancer in Irish RTRs have influenced the national incidence of skin cancer. The high incidence of SCC, basal cell carcinoma and Bowen's disease in the early post-transplant period for older patients and the cumulative risk in younger patients with increased duration of transplantation highlight the importance of implementing early and continued cancer surveillance regimens post-transplant.

Correspondence
Fergal J. Moloney.
E-mail: fergalmoloney@eircom.net

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In the past 30 years there have been more than 100 studies attesting to the escalating problem of skin cancers in renal transplant recipients (RTRs). As increasing numbers of patients are transplanted, graft survival improves and the average age at transplant gets older, the incidence of post-transplantation cancers has increased, in particular nonmelanoma skin cancer (NMSC), the commonest cancer following transplantation.[1] Accurate determination of the incidence of post-transplant malignancies plays a vital role in planning resources to tackle this problem and developing targeted prevention strategies.

Despite the many studies in this area, there are limitations to the conclusions that may be drawn from the large cancer surveillance systems and the single-centre studies that have attempted to quantify the extent of post-transplant carcinogenesis. Single-centre studies are often retrospective and do not provide information on person-years of follow-up. As such,

they cannot provide a true estimate of cancer risk based on incidence. Few countries with national cancer registries (primarily in Europe) can accurately compare skin cancer rates in a subgroup, such as RTRs, with the national rate.

Since 1994, the Irish National Cancer Registry has registered all histologically confirmed skin cancers including squamous cell carcinoma (SCC), basal cell carcinoma (BCC), malignant melanoma and preinvasive skin cancers for the largely homogeneous population of the Republic of Ireland. The registry records each individual occurrence of skin cancer in each patient. Provided that sites of the cancers were more than 5 cm apart and clearly not metastatic, each cancer, even of the same histological type, is counted. This is particularly relevant when comparing standardized incidence ratios (SIRs) between the national population and a transplant population, where many patients have multiple NMSCs.

Many registries do not record BCC or preinvasive lesions. Others record first NMSC only and classify multiple lesions as a single record. The ANZDATA registry policy of recording first NMSCs only resulted in an underestimation by 28·4% of the number of NMSCs in a transplant patient group.[2]

This diversity of registration practices is also reflected in differing systems of data collection. Reporting of cancers to the national registry is a legal obligation in Sweden, while in some countries it is voluntary but passive, and others employ tumour registration staff in active registration of all cancers. The latter active registration policy exists in Ireland where state-funded staff actively collect histological data from hospitals, pathology laboratories and general practitioners, ensuring comprehensive and accurate data relating to the national incidence of skin cancer.

Materials and methods

Beaumont Hospital is the national renal transplant centre in Ireland. All RTRs are entered into a national database in the hospital maintained by dedicated personnel. All renal transplants carried out in the Republic of Ireland since 1986 were matched with Irish National Cancer Registry records of cancers incident from 1994 to 2001 inclusive.

The study population comprised a cohort of patients who received renal transplants between 8 January 1986 and 31 December 2001. Of these, 107 had died before the study period and 42 had insufficient information for matching with the cancer registry data. The remaining 1755 transplants were performed on 1558 patients, 995 (64%) males and 563 (36%) females. These patients were matched against all registrations of cancer during the study period of 1 January 1994 to 31 December 2001.

Incidence rates were calculated as SIRs, where the observed numbers were all cancers in the transplant cohort incident during the study period and expected numbers were calculated from the product of the average national age-specific incidence rates for 1994–2001 and the number of person-years at risk. Poisson confidence intervals were calculated using standard methods.[3] Direct standardization methodology using the European standard population was further employed to control for differences in the age structure between skin cancer patients in the transplant and nontransplanted populations. The period of risk was calculated from 1 January 1994 or the date of transplant, whichever was the later, to the end of follow-up (31 December 2001 or death). Patients whose transplant failed and were recommenced on dialysis were still classified in the analysis as 'at risk'. The duration of immunosuppression was calculated from the date of transplant to the end of the study period, the date of transplant failure when dialysis was recommenced or the date of death, whichever was the earliest. Multiple episodes of immunosuppression were aggregated.

Results

The mean age of transplant patients was 40 years (median 41) (Table 1). Most patients were on triple immunosuppression with ciclosporin, azathioprine and steroids. The median duration of immunosuppression was 5·35 years. The most frequent duration of immunosuppression was < 4 years, but 9% of patients had been transplanted for more than 12 years. The median period at risk was 5·72 years. Most patients (69%) were at risk for the full study period, while the remaining 31% were either transplanted after 1 January 1994 or died prior to the end of the study period (31 December 2001).

All cancers

During the study period, the National Cancer Registry documented 751 cancers in 257 patients. Of these, 49 had occurred prior to transplant and were excluded from analysis, leaving 702 cancers in 219 patients. This gave a cumulative incidence rate of 12% for all cancers after 12 years of

Table 1 Renal transplant patients included in the study

	Females		Males	
	Number	% of total	Number	% of total
Age at transplant (years)				
< 30	173	31%	243	24%
30–39	107	19%	222	22%
40–49	109	19%	206	21%
50–59	105	19%	195	20%
60 and over	69	12%	129	13%
Duration of immunosuppression (years)				
0–4	231	41%	374	38%
4–8	144	26%	311	31%
8–12	136	24%	223	22%
12–16	52	9%	87	9%
Period at risk (years)				
0–4	212	38%	375	38%
4–8	162	29%	326	33%
8–12	189	34%	294	30%
All patients	563		995	

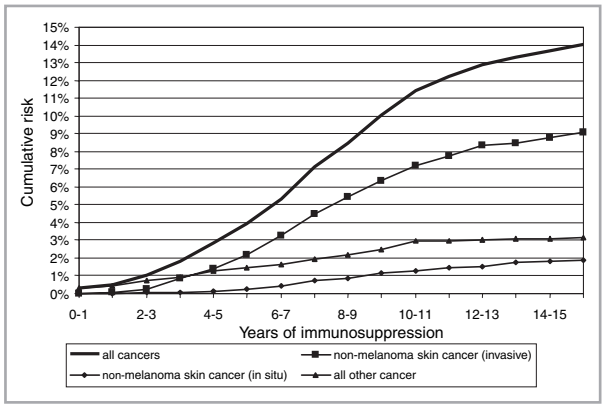

Fig 1. Cumulative rate of incidence of cancer.

immunosuppression, and 14% overall (Fig. 1). The incidence rates for NMSC (both invasive and noninvasive), carcinoma *in situ* of the cervix, lung cancer, renal cancer and lymphoma were all significantly greater than expected (Table 2).

Skin cancer

Most of the cancers (88%) were NMSCs, either malignant (69%) or *in situ* (19%). The expected number of malignant NMSCs in the transplant patients was 15, but 487 were found during the study period, giving an SIR of 33·3 ± 3·0 (Table 2). These 487 NMSCs represent 1·0% of the NMSCs registered nationally for the same period, 1·6% of those in males and 0·2% of those in females. The SIR of 65 for *in situ* skin cancer was even greater than that for invasive NMSC and represented 1·6% of all *in situ* NMSCs in Ireland during the study period. At 10 years of immunosuppression, 6·4% of patients had developed invasive NMSC, and 1·2% had developed *in situ* NMSC (Fig. 1). There were five melanomas recorded for the period at risk, all occurring in males at a mean of 6 years (range 3–10) post-transplantation. This represented a sevenfold increase in invasive malignant melanoma of the skin in men, falling short of statistical significance due to low numbers. The high SIR for Kaposi sarcoma (SIR = 97) was also nonsignificant, again reflecting small numbers.

Age and duration of immunosuppression

The risk of skin cancer increased with age. The largest number (184; 38%) of invasive skin cancers was diagnosed in the 50–59-year age group. The mean age at transplant was 40·3 years compared with the mean age at incidence of NMSC in this cohort of RTRs (51·1 years), reflecting the lag phase between transplant and skin cancer development. The development of *in situ* SCC at a younger mean age (50·7 years) points to the potential invasive nature of these lesions with time. The median duration of exposure to immunosuppression was 4·6 years and the mean 5·2 years. Nineteen per cent of patients had been on immunosuppressive therapy for < 1 year and no patient had been on therapy for > 16 years. The mean duration of immunosuppression was 5·2 years for all transplant patients compared with 8·2 years for transplant patients who

Table 2 Cancer numbers and standardized incidence ratio (SIR) for all cancer types

	Cancers				SIR (95% confidence interval)		
	Males	Females	Both	% of total	Males	Females	Both
All cancers	583	119	702		**18·0 (16·6–19·5)**	**6·3 (5·1–7·4)**	**13·7 (12·7–14·7)**
Nonmelanoma skin	431	56	487	69·3%	**41·4 (37·5–45·3)**	**13·3 (9·8–16·7)**	**33·3 (30·3–36·2)**
Carcinoma *in situ* of skin	109	26	135	19·2%	**101·8 (82·7–121·0)**	**25·5 (15·7–35·3)**	**64·6 (53·7–75·5)**
Carcinoma *in situ* of cervix	0	9	9	1·2%		**5·3 (1·8–8·8)**	
Kidney	3	3	6	0·8%	5·0 (0·0–10·7)	18·3 (0·0–38·9)	**7·9 (1·6–14·2)**
Lymphoma	7	3	10	1·4%	**9·2 (2·4–15·9)**	9·0 (0·0–19·2)	**9·1 (3·5–14·8)**
Lung	8	2	10	1·4%	2·6 (0·8–4·3)	2·3 (0·0–5·6)	**2·5 (1·0–4·1)**
Unknown primary site	4	2	6	0·8%	4·0 (0·1–8·0)	4·5 (0·0–10·7)	4·2 (0·8–7·5)
Melanoma of skin	5	0	5	0·7%	6·6 (0·8–12·3)	0·0	3·3 (0·4–6·3)
Breast	0	3	3	0·4%	0·0	0·8 (0·0–1·7)	0·8 (0·0–1·7)
Corpus uteri	0	3	3	0·4%		6·2 (0·0–13·1)	
Cervix	0	3	3	0·4%		7·2 (0·0–15·3)	
Ovary	0	3	3	0·4%		4·4 (0·0–9·4)	
Kaposi sarcoma	1	1	2	0·3%	50·9 (0·0–150·7)	922·0 (0·0–2729·2)	96·5 (0·0–230·2)
Liver	2	0	2	0·3%	13·0 (0·0–31·0)	0·0	10·7 (0·0–25·5)
Multiple myeloma	2	0	2	0·3%	6·5 (0·0–15·6)	0·0	4·8 (0·0–11·4)
Pancreas	2	0	2	0·3%	4·1 (0·0–9·8)	0·0	2·8 (0·0–6·7)
Leukaemia	0	2	2	0·3%	0·0	12·9 (0·0–30·9)	3·5 (0·0–8·4)
Prostate	0	0	0	0%	0·0		
Colorectal	2	0	2	0·3%	1·0 (0·0–2·3)	0·0	0·7 (0·0–1·7)
All other	7	3	10	1·4%	1·0 (0·0–2·3)	0·0	0·7 (0·0–2·7)

Figures in **bold** are significantly higher ($p < 0·05$) than expected.

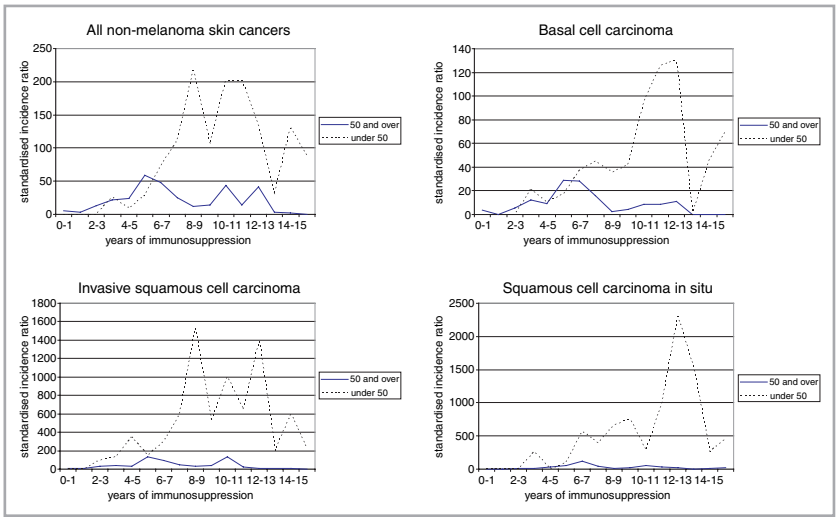

Fig 2. Standardized incidence ratio for nonmelanoma skin cancer, by duration of immunosuppression.

developed skin cancer. There was a significant increase in skin cancer incidence at all periods post-transplant (Fig. 2). There was a significant excess of observed over expected cases even for the shortest period of exposure to immunosuppressive therapy. However, this excess risk appeared to be confined to the older patients, and to be greater in the first than the second year of immunosuppression. For the older patients, risk of skin cancer increased steadily from the second to the sixth year of immunosuppression, and remained constant from then on, with some irregularity due to the small numbers. For patients aged < 50 years there was little excess risk in the earlier years. No skin cancers were diagnosed in this group in the first 3 years, and only eight in total until the sixth year of immunosuppression. However, after this time the relative risk rose very rapidly, and at 8 years of immunosuppression was more than 200 times that of a group of similar age in the general population. Direct age standardization for all NMSCs illustrates how the secondary peak incidence rate for RTRs aged 50+ years corresponds closely with the peak incidence rate for RTRs aged < 50 years (Fig. 3). For periods of more than 12 years of immunosuppression the numbers were quite small and the effects of random variation predominate. All morphological types showed similar trends with duration of immunosuppression, with low rates in the earlier years, rising to a peak at 5 years of immunosuppression for older patients and at 8–10 years in those aged < 50 years, with constant, but randomly fluctuating, risk thereafter.

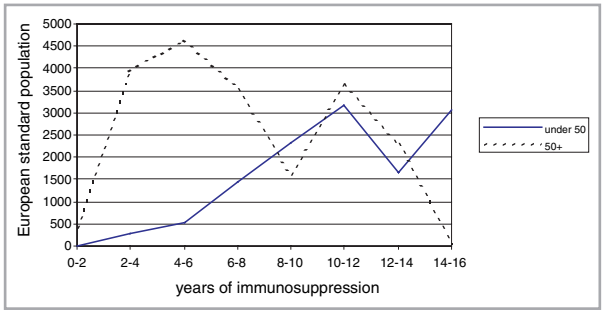

Fig 3. Direct standardization. All invasive nonmelanoma skin cancers standardized to the European standard population by years of immunosuppression.

Morphology

Most of the skin cancers registered were SCC, invasive (50%) or *in situ* (22%), occurring over twice as frequently as BCC (27%). This differed from the general population, where BCC makes up 58% of all NMSC, and SCC (invasive and *in situ*) 40%. Overall, the excess risk of SCC for the transplant population was much greater than the excess risk of BCC (Table 3). The invasive SCC/BCC ratio was much higher for men than for women. The highest SIR was a 105-fold increase in the incidence of *in situ* SCC for men, and the lowest a sevenfold increase in the incidence of BCC for women. For women the invasive SCC/BCC ratio was 1·2, while for men it was 2·0. However, SCC *in situ* made up a larger percentage of the total for women, and when both malignant and *in situ* forms were combined, the SCC/BCC ratio for women was 2·4, compared with 2·8 for men. The age profile for SCC (both invasive and *in situ*) and BCC was similar, with the largest number of cases for men in the 50–59-year age group and for women in the 60–69-year group.

Nonmelanoma skin cancer subsites

The SIR for invasive NMSC was well above 1 for all skin subsites, but there was substantial variation (Fig. 4). A similar pattern was found for *in situ* SCC. The highest SIR was in the scalp and neck (SIR = 67 ± 15) and the upper limb (SIR = 59 ± 13). There was a high incidence of 'overlapping sites' (SIR = 66 ± 21) where the cancer extended over more than one anatomical site, pointing to a tendency in RTRs to develop larger, more extensive skin cancers. There were slightly more cancers on the right arm (34 cancers, 57%) than the left (26 cancers, 43%) but this difference was not statistically significant ($P = 0{\cdot}20$). Sun-protected areas such as the

Table 3 Morphological types of nonmelanoma skin cancer

	Observed cases						SIR (± 95% confidence interval)		
	Males		Females		Both				
	Cases	% of total	Cases	% of total	Cases	% of total	Males	Females	Both
SCC	282	52%	31	38%	313	50%	90 ± 11	45 ± 16	82 ± 9
BCC	143	26%	25	31%	168	27%	20 ± 3	7 ± 3	16 ± 2
SCC in situ	112	21%	24	30%	136	22%	105 ± 19	24 ± 9	65 ± 11
Nonspecific	2	0%	0	0%	2	0%	20 ± 28	–	15 ± 21
Other	2	0%	1	1%	3	0%	2 ± 3	1 ± 3	2 ± 2
All	541		81		622		44 ± 4	14 ± 3	34 ± 3

SIR, standardized incidence ratio; SCC, squamous cell carcinoma; BCC, basal cell carcinoma.

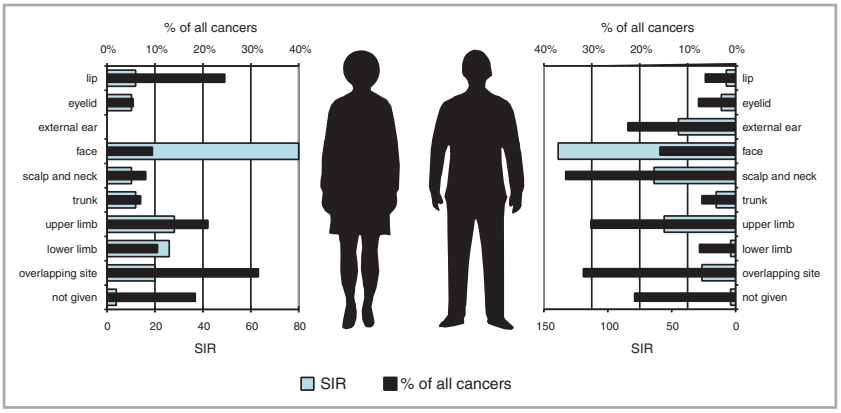

Fig 4. Distribution of nonmelanoma skin cancer, by sex. SIR, standardized incidence ratio.

trunk (SIR = 15 ± 7) and lower limb (SIR = 14 ± 8) had much smaller increases in NMSC risk relative to the general population. There were no external ear NMSCs and only three scalp and neck NMSCs recorded in females over the study period. This contrasted with 56 NMSCs of the ear and 78 on the scalp and neck in their male counterparts, a strong indication of how hairstyles and hair thickness influence ultraviolet (UV) exposure.

Discussion

For this cohort of RTRs we have related skin cancer risk directly to total duration on immunosuppressive therapy and period at risk for each individual patient. The time dependence of risk is striking, and displays different patterns for patients under and over 50 years of age. For the older patients there was a modest increase in skin cancer risk in the first year post-transplant. This is a well-known phenomenon of any screening or surveillance system, where cancers which would otherwise have been detected symptomatically over a number of years are all picked up in a relatively short period, giving a transient increase in apparent incidence, followed, as is seen here, by a return to baseline levels. Following this 'prevalence surge', the relative risk of cancers for the older patients rose quite rapidly, to a peak at about 6 years after transplant. This may represent an early proliferation of UV radiation-damaged clones that had previously been held under immune control. The much later rise in incidence in younger patients, peaking at 10–12 years after transplant, and at a much higher relative rate, is more likely to be due to cancers arising from new mutations. A similar, but much smaller rise in relative incidence is seen for the older patients at the same time post-transplant. The very high rate of cancer incidence in RTRs aged < 50 years implies that potentially malignant change occurs in the skin at a rate over 200 times greater than the observed incidence of NMSC. The majority of this malignant change appears to give rise to clones which are detected and removed by the immune system. However, the observations in older patients suggest that a fraction of the malignant clones, possibly 10%, is not eliminated, but remains in a dormant or very slowly growing state under immune surveillance, and grows rapidly once this surveillance is lifted. This phenomenon is seen in patients of all ages, but is less easily identified in the younger patients because of the very low background level of cancer.

It would be expected that relative risk would increase as much in older patients as in the younger at 10–12 years post-transplant, but this was not seen. However, the absolute risk at 10–12 years was the same for both age groups, and the lower relative risk for the older patients was due to the higher rate in the older normal population. This fall in relative risk, but not in absolute risk, suggests that the difference in

immune status between RTRs and the normal population reduces with age, due to the gradual failure of immune surveillance.[4] This decline in immune surveillance would partly explain the exponential increase in skin cancer risk with age; however, the parallel policy of gradually reducing the total immunosuppressive load in long-term stable RTRs must also be taken into account. It is also possible that the development of skin cancer later in life is due to trigger events happening much earlier, leaving only a limited number of skin cancer cells with malignant potential, most of which have already been removed by immune surveillance in the older patients.

Exposure to UV radiation activates proto-oncogenes and/or inactivates tumour suppressor genes in keratinocytes, thereby initiating and promoting the development of SCC.[5] Damage to DNA appears to be one of the triggering events in inducing systemic immunosuppression via the release of immunosuppressive cytokines and mediators.[6] Studies show how skin tumours in adult mice exposed to UVB were rejected when transplanted to healthy mice but continued to grow when transplanted to mouse skin pre-exposed to UVB radiation.[7] The addition of immunosuppressive drugs amplifies the damaging effect of UVB by depleting dermal immune surveillance cells, increasing the risk of human papillomavirus (HPV) infection and inactivating the tumour suppressor gene p53 protein which further affects the repair of UV-damaged cells. Recent work identifies an association specifically with the epidermodysplasia verruciformis HPV types and the development of SCCs of the skin.[8] Long duration of exposure to immunosuppression is an independent risk factor for the development of skin cancer post-transplantation.[9–13] However, this study highlights the aetiological effect of exposure to UV radiation which acts not only in the initiation and promotion but also in the progression of these skin cancers.[14] The pattern of skin cancer observed in RTRs is consistent with the principal aetiological role of UV radiation. Skin cancers in RTRs show the same age dependence, and the same anatomical distribution by sex, as in the general population. Figure 4 illustrates the association between invasive NMSC post-transplant and the UV exposure of habitually exposed sites. Male RTRs are at particular risk of invasive SCC of the scalp, neck and external ear. Female RTRs, with less frequent outdoor occupations and more natural protection from hair at these sites, have a significantly lower risk. RTRs most likely to develop SCCs are those with clinically evident UV damage, in particular actinic keratosis. This study is based on comparisons of age-standardized incidence rate, which is a more appropriate and valid measure of risk for skin cancer than cumulative incidence.[15] Skin cancer is strongly age dependent, so by using age-standardized rate calculations we corrected for the ageing of the cohort and also for varying periods at risk due to early death or late entry into the study. Estimates of cumulative incidence of NMSC in RTRs at 10 years range from 4·8% in Germany[13] to 24·8% in subtropical Queensland.[9] Although varying latitudes, population demographics and registration methods may explain some of these differences, studies of neighbouring populations in Southern Europe found 10-year NMSC cumulative incidence rates of 10·8%[10] and 48%,[16] respectively. Cumulative incidence cannot be compared between populations without correction for the age structure of the transplanted cohort.

After transplantation, the age-standardized incidence of cancer relative to the nontransplanted population was significantly increased for a number of noncutaneous cancers (Table 2). Skin cancer, however, remains the most common post-transplant malignancy, with a rate 50 times that in the general population. The 6·6-fold increase in melanoma risk relative to the general population fell short of statistical significance at the 95% level of confidence. Jensen *et al.* found a three-to-fourfold increase in melanoma incidence post-transplant; however, Lindelof *et al.*, with a larger study population, recorded no statistically significant increase relative to the general population.[11,17] Increases in Kaposi sarcoma (97-fold) in our patient population represent a large increase from the expected; however, the numbers were too small for accurate statistical analysis. For rare tumours such as Merkel cell tumours and sebaceous carcinoma, anecdotally reported to be increased post-transplant,[18,19] larger numbers from multicentre studies would be required before comparisons with national figures can be performed. We had speculated whether increasing national incidence rates for NMSC could in part be explained by the emerging problem of post-transplant NMSC.[20–24] Again, allowing for differing methodologies, latitudes and durations, studies over past decades have shown annual percentage increases in incidence of SCC ranging from 2% to 7% in males and from −1% to 6% in females.[25] In our study, the NMSCs recorded in RTRs over the 8-year study period represent 1·6% of all male and 0·2% of all female NMSCs registered nationally for the same period. These figures suggest that transplant-associated NMSCs have contributed substantially to global increases in skin cancer incidence, particularly since the advent of triple drug immunosuppression in the early 1980s.

The reversal of the normal BCC/SCC ratio following transplantation in Ireland has similarly been demonstrated in Scandinavia and Australia. This reversal was not seen in studies from Spain and Italy, where BCC remained the most common skin cancer post-transplant.[10,16] These ratios reflect differences in genetic backgrounds, skin types and sun exposure habits at different latitudes. While the cancer registry records all episodes of *in situ* SCC, it is recognized that many cases are treated with destructive techniques where no histological confirmation is sought and may escape registration. The number of cases of Bowen's disease ($n = 135$) is thus likely to be an underestimation of the incidence in this transplant population.

In summary, this study highlights the increased risk of NMSC post-transplant, in males, with age, and with longer duration immunosuppression. A new era of transplantation has increased the mean age at transplant and dramatically improved both patient and graft survival post-transplant. The consequent longer duration on immunosuppressive agents, however, has increased the incidence of long-term transplant complications and could potentially herald a further upsurge in post-transplant malignancies. We have shown how the

burden of post-transplant NMSC has already impacted on the population incidence of NMSC in Ireland. As newer immunosuppressive agents may prove less carcinogenic than their predecessors,[26] reliable incidence figures are needed to monitor trends in NMSC rates and to assess the effectiveness of skin cancer education and prevention programmes. For RTRs aged 50+ years, cancer risk manifests within the first years post-transplant. This study emphasizes the need for all transplant patients to be screened pretransplant, risk categorized, educated and followed up accordingly.

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