Cutaneous Melanoma Is Related to Immune Suppression in Kidney Transplant Recipients

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Abstract

Melanoma incidence is increased after organ transplantation, but there is uncertainty as to why this occurs. Diagnoses of invasive melanoma were ascertained in 8,152 kidney transplant recipients (1982-2003) by linking national Australian population-based registers, the Australia and New Zealand Dialysis and Transplant Registry, and the Australian National Cancer Statistics Clearing House. Incidence rate ratios (IRR) and standardized incidence ratios were used to compare melanoma risk during periods of transplant function and failure. Standardized incidence ratios were also computed by time since transplantation. Risk factors were examined using multivariate Poisson regression. Linkage identified 82 melanomas (134/100,000 person-years). Incidence was lower after resumption of dialysis and reduction of immune suppression than during transplant function [IRR, 0.09; 95% confidence interval (95% CI), 0.01-0.66]. During first transplant function, melanoma (n = 74) relative risk peaked in the second year and declined linearly thereafter (P trend = 0.03). During first transplant function, risk was positively associated with increasing year of age (IRR, 1.05; 95% CI, 1.03-1.07) and receipt of lymphocyte-depleting antibody (IRR, 1.73; 95% CI, 1.05-2.84). Female sex (IRR, 0.57; 95% CI, 0.35-0.94), non-Caucasian race (IRR, 0.15; 95% CI, 0.02-1.05), and increasing time since transplantation (P trend = 0.06) were inversely associated with risk. The incidence pattern and risk factor profile for melanoma after transplantation strongly suggest that the current receipt, intensity, and possibly the recency of iatrogenic immunosuppression increase melanoma risk. Melanoma risk was also associated with proxy indicators of high personal sun exposure and sensitivity. These findings show the marked influence of immunologic control over melanoma incidence. (Cancer Epidemiol Biomarkers Prev 2009;18(8):2297–303)

Introduction

It has long been appreciated that intact immune function may be important in preventing the emergence of cutaneous melanoma (1-4). A meta-analysis of population-based data has shown an increased incidence of melanoma in both solid organ transplant recipients (meta-SIR 2.3) and people with HIV/AIDS (meta-SIR 1.2; ref. 5), indicating an association between melanoma risk and immune deficiency. Further support for a role of immune suppression comes from the observation of an excess of the precursor lesion, acquired melanocytic nevi, in immune-suppressed populations, including pediatric and adult transplant recipients (6, 7), individuals with HIV/AIDS (8), and chemotherapy recipients (9). However, because individual population-based studies have identified only small numbers of melanomas in these immune-deficient populations, there is uncertainty about the immune-related factors responsible for this association (10).

To investigate the role of immunosuppression in the etiology of cutaneous melanoma we studied the incidence of and risk factors for this neoplasm in a large, population-based, Australian cohort of kidney transplant recipients. Immune-related factors under evaluation included the current receipt of iatrogenic immunosuppression, as well as the intensity, duration, and type of immunosuppression.

Materials and Methods

Study Population. The study cohort and method of cancer ascertainment have been described previously (11, 12). Briefly, the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry contains comprehensive

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Note: The interpretation and reporting of the data are the responsibility of the authors and in no way should be seen as official policy or interpretation of the ANZDATA Registry.

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Table 1. Characteristics of the Australian kidney transplantation cohort

Characteristics	No. (%) patients	Person-years*	
		Total	Mean (SD)
Age at receipt of first transplant (y)			
≤35	2,612 (32)	17,150	6.6 (5.4)
36-49	2,738 (34)	17,005	6.2 (5.3)
≥50	2,802 (34)	14,891	5.3 (4.6)
Sex			
Male	4,817 (59)	28,878	6.0 (5.1)
Female	3,335 (41)	20,168	6.0 (5.2)
Racial origin			
Caucasian	7,201 (88)	44,369	6.2 (5.2)
Australian Aboriginal or Torres Strait Islander	295 (4)	1,202	4.1 (3.9)
Asian	440 (5)	2,450	5.6 (4.8)
Pacific Islander	69 (1)	285	4.1 (3.6)
Middle Eastern	31 (0)	163	5.3 (4.8)
Other	116 (1)	575	5.0 (4.1)
Primary end-stage renal disease			
Diabetic nephropathy	803 (10)	4,193	5.2 (4.6)
Glomerulonephritis	2,923 (36)	17,225	5.9 (5.2)
Hypertensive and arteriopathic	483 (6)	2,758	5.7 (5.0)
All other and unknown	3,943 (48)	24,870	6.3 (5.2)
State of residence at entry into ANZDATA			
New South Wales	2,635 (32)	15,953	6.1 (5.3)
Victoria	2,078 (25)	12,767	6.1 (5.2)
Queensland	1,447 (18)	8,735	6.0 (4.8)
Western Australia	758 (9)	4,694	6.2 (5.5)
South Australia	826 (10)	4,792	5.8 (4.9)
Tasmania	132 (2)	772	5.8 (4.5)
Australian Capital Territory	195 (2)	1,079	5.5 (4.6)
Northern Territory	81 (1)	253	3.1 (3.0)
Calendar year at receipt of first transplant			
Before 1986	1,244 (15)	10,117	8.1 (7.4)
1986-1995	3,763 (46)	29,485	7.8 (4.8)
1996 or later	3,145 (39)	9,443	3.0 (2.1)

*Person-years during first functioning transplant.

information on all patients who commence maintenance dialysis or receive a kidney transplant in Australia and New Zealand (13). Demographic and clinical information are reported directly to the Registry by transplantation units. For this analysis, the cohort was restricted to Australian residents on the ANZDATA Registry who had received their first transplant between January 1, 1982 and September 30, 2003, and who had no prior diagnosis of cutaneous melanoma, for a total of 8,152 patients.

Data Collection. Data on the first primary melanoma were ascertained by record linkage with the National Cancer Statistics Clearing House (14), which is a compilation of data from the eight Australian population-based cancer registries to which all cases of primary invasive cancer, except nonmelanoma skin cancer, are reported by statute. Record linkage was done using an established probabilistic technique, and all diagnoses within the ICD10 C43 rubric were ascertained. General population melanoma incidence rates were also obtained by 5-year age group, sex, calendar year, and state/territory, for each year since 1982. Ethical approval was obtained from all relevant institutional ethics committees.

Statistical Analysis

Melanoma Incidence Pattern. For each patient, person-years (PY) of follow-up were accumulated from the date of first transplantation until the date of first melanoma diagnosis, death, last contact, or the latest date to which cancer data were available, whichever occurred first. The incidence of melanoma was calculated for periods of transplant function, when people are in receipt of immunosuppression, and during periods of dialysis subsequent to transplant failure, when immunosuppression is usually substantially reduced, and in those whose kidney is removed, stopped completely (15). For this analysis, the first 3 mo of each period were disregarded, as melanomas diagnosed within this time would almost certainly have developed in the preceding period (12).

Poisson regression modeling was used to calculate incidence rate ratios (IRR) with 95% confidence intervals (95% CI) comparing the incidence of melanoma during each period relative to that during the first functioning transplant, adjusted for age, sex, and duration of transplant function (years).

Standardized incidence ratios (SIR) of melanoma, using age-specific, sex-specific, calendar year–specific, and state/territory-specific population melanoma incidence rates, were also computed for each posttransplantation period. Additionally, on the basis of the distribution of melanomas by time since transplantation, SIRs were computed for 6 periods of time during the first functioning transplant (<1, 1-1.99, 2-4.99, 5-9.99, 10-14.99, and ≥15 y). A test for linear trend across these exposure periods was done by using Poisson maximum likelihood regression. $P < 0.05$ was considered statistically significant.

Melanoma Risk Factors. Risk factors for melanoma during the first functioning transplant were examined using data reported to the ANZDATA Registry. Self-reported race (Caucasian, non-Caucasian) and sex were considered proxy indictors of cutaneous sun sensitivity and exposure

to solar UV radiation, respectively. A proxy indicator of ambient solar UV radiation, residential latitude at entry into ANZDATA, was classified into one of three bands that broadly demarcate Australia's most populous cities, namely, Brisbane, Sydney, and Melbourne. The receipt of individual immunosuppressive agents was recorded in the Registry at 1, 2, 3, 6, 12, 24, 36, and 60 mo posttransplantation, and at 5-year intervals thereafter. Using these data, a time-dependent variable was constructed to represent the current receipt of each immunosuppressive agent with sufficient follow-up time: the calcineurin inhibitors cyclosporine and tacrolimus, and the antiproliferatives azathioprine and mycophenolate. A time-dependent variable was also constructed for current receipt of each of the two classes of agents, calcineurin inhibitors and antiproliferative agents. Receipt of the steroid prednisolone was not examined given its near universal (95%) use within the cohort. Patients for whom the type of immunosuppressive agent was unknown at two or more consecutive time points (n = 336; 4.1%; none with melanoma) were excluded from the risk factor analyses.

The other immunosuppression-related factors examined were duration of continuous receipt of immunosuppressive agents, or time since transplantation, and exposures reflective of the degree or intensity of immunosuppression. These included the receipt of T lymphocyte–depleting agents for induction immunosuppression or for treatment of acute graft rejection, specifically, the polyclonal antibodies antithymocyte/antilymphocyte globulin and the monoclonal antibody anti-CD3 agent muromonab-CD3; donor source; the number of human leukocyte antigen mismatches between the recipient and the donor; and the receipt of a different organ transplant in addition to a kidney, either at the time of, or after, kidney transplantation (time-dependent, yes/no). Other factors examined were current age (time-dependent, single years), a history of cancer other than melanoma recorded in the National Cancer Statistics Clearing House prior to transplantation, cause of primary renal disease leading to renal failure, and the number of years of dialysis prior to first transplantation.

Poisson regression modeling was used to determine IRR with 95% CI for each risk factor. All variables with two-sided statistical significance ($P < 0.10$) in univariate analysis were considered in the multivariate analysis. The final multivariate model was determined using a forwards stepwise approach and included only those covariates with two-sided statistical significance ($P < 0.05$) after adjustment for each other and for age, sex, time since transplantation, and the current receipt of each immunosuppressive agent or class of agents, which were included *a priori*. Statistical interaction was assessed between the receipt of calcineurin inhibitors and T-cell-depleting antibodies. All analyses were done using Stata version 10 (StataCorp LP).

Results

Study Cohort. The study cohort consisted of 8,152 eligible patients, with 61,272 PY of follow-up after transplantation (Table 1), including 49,046 PY during the first functioning transplant. The median age at first kidney transplantation was 43 years (range, 1-78 years). A single transplant was received by 7,353 (90%) patients, whereas 717 (9%) received two and 82 (1%) received three or more transplants. Most patients (81%) had at some stage received combination therapy with calcineurin inhibitors and antiproliferative agents, and 1,827 (22%) were administered T-cell–depleting antibodies (48% antithymocyte/antilymphocyte globulin, 59% muromonab-CD3). Antibodies were mostly (63%) administered for the treatment of acute rejection, at a median of 12 days posttransplantation.

Melanoma Incidence. A total of 82 incident cutaneous melanomas were identified after transplantation, and the age- and sex-adjusted incidence was 134 per 100,000 PY (95% CI, 108-166). The median time to diagnosis was 4 years after transplantation, and no melanomas were diagnosed within the first 3 months of transplantation or return to dialysis.

Nearly all melanomas were diagnosed during periods of transplant function: 74 (90%) during the first functioning transplant, 1 (1%) after first transplant failure and return to dialysis, 6 (7%) during a higher-order transplant, and 1 (1%) after higher-order transplant failure and return to dialysis (Table 2). Melanoma incidence was significantly lower during dialysis subsequent to failure of the first transplant than during the first functioning transplant (IRR, 0.09; 95% CI, 0.01-0.66; P = 0.018). Incidence during higher-order transplant function was not significantly different from that during the first functioning transplant (IRR, 1.22; 95% CI, 0.53-2.84; P = 0.64). Upon failure of the first functioning transplant, melanoma incidence (17/100,000 PY; 95% CI, 2-121) returned to a rate similar to that observed during dialysis prior to transplantation (86/100,000 PY; 95% CI, 65-113). The SIRs followed the same pattern for the periods of transplant function and failure (Table 2).

During the first functioning transplant, melanoma incidence peaked in the second year (SIR, 4.57; 95% CI, 2.50-7.67; Fig. 1), and rates were significantly elevated compared with the general population up to 10 years

Table 2. Incidence of cutaneous melanoma by transplant function

Transplant function	O (E)	PY	Crude rate/100,000 PY (95% CI)	SIR (95% CI)	IRR*(95% CI)	$P^{\dagger}$
First transplant functioning	74 (27.04)	47,177	157 (125-197)	2.74 (2.15-3.44)	1.00	
First transplant failed, dialysis re-instituted	1 (2.99)	5,880	17 (2-121)	0.34 (0.01-1.89)	0.09 (0.01-0.66)	0.018
Higher-order transplant functioning	6 (2.12)	4,418	136 (61-302)	2.83 (1.04-6.15)	1.22 (0.53-2.84)	0.640
Higher-order transplant failed, dialysis re-instituted	1 (0.49)	1,189	84 (12-597)	2.05 (0.05-11.41)	0.54 (0.08-3.94)	0.546

NOTE: All calculations exclude follow-up and incident cancers during first 3mo of each period; by definition this also excludes patients who died within the first 3 mo of transplantation (n = 249) and patients with early transplant failure who died within 3 mo of reinstitution (n = 117) of dialysis.
Abbreviations: O, observed; E, expected.
*Adjusted for current age (years), sex, cumulative duration of transplant function (years).
†P value for difference with first functioning transplant.

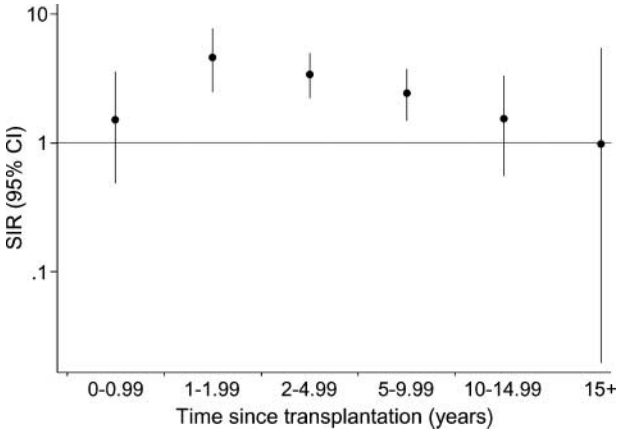

Figure 1. Standardized incidence ratio for cutaneous melanoma by time since transplantation during the first functioning transplant.

posttransplantation. After the second-year peak, the SIR declined linearly towards unity (P trend = 0.03).

During the first functioning transplant, 22 (30%) of melanomas were diagnosed in recipients ages 22 to 50 years, 27 (36%) in recipients ages 51 to 60 years, and 25 (34%) in recipients ages 61 to 74 years. The morphology of 37 (50%) melanomas diagnosed during the first functioning transplant was unspecified. Of the remainder, 27% (n = 20) were superficial spreading melanomas, 7% (n = 5) were nodular melanomas, and 16% (n = 12) were of other specified morphology.

Melanoma Risk Factors during Transplant Function. In multivariate modeling, the risk of incident cutaneous melanoma during the first functioning transplant was not significantly associated with receipt of any of the individual immunosuppressive agents. As the adjusted point estimate for azathioprine (IRR, 2.06; 95% CI, 0.88-4.81) was similar to that for mycophenolate (IRR, 2.45; 95% CI, 0.91-6.59), and that for cyclosporine (IRR, 1.39; 95% CI, 0.73-2.67) was similar to that for tacrolimus (IRR, 1.28; 95% CI, 0.33-5.00), current receipt of the class of agent, antiproliferative or calcineurin inhibitor, respectively, was included in the final model.

Melanoma risk was positively associated with increasing year of age (IRR, 1.05; 95% CI, 1.03-1.07) and receipt of T lymphocyte–depleting antibody (IRR, 1.73; 95% CI, 1.05-2.84; Table 3). Risk estimates were similar for recipients of only polyclonal (41% of antibody recipients) or monoclonal antibody (52%; data not shown). Female sex (IRR, 0.57; 95% CI, 0.35-0.94), non-Caucasian race (IRR, 0.15; 95% CI, 0.02-1.05), and increasing time since transplantation (P trend = 0.06) were inversely associated with risk. Risk was not significantly associated with receipt of an antiproliferative (IRR, 2.16; 95% CI, 0.93-5.03) or calcineurin inhibitor (IRR, 1.42; 95% CI, 0.75-2.71). There was no significant interaction between receipt of a calcineurin inhibitor and a T lymphocyte–depleting antibody (P = 0.384). Risk was significantly increased in those with a cadaveric/nonrelated donor in univariate, but not in multivariate analysis. Melanoma risk was not associated with residential latitude at entry into ANZDATA.

Discussion

In this large, population-based analysis of kidney transplant recipients, cutaneous melanoma risk was associated with the current receipt and intensity of iatrogenic immunosuppression. The effect of immune suppression was reversible in that increased melanoma risk was confined to periods of transplant function. After transplant failure, when immune suppression is substantially reduced or completely withdrawn (15), risk returned to baseline level. Melanoma risk was greatest in the second year of graft function and declined linearly thereafter. During transplant function, melanoma risk was positively related to receipt of a T lymphocyte–depleting antibody, and proxy indicators of high personal sun exposure and high sun sensitivity. The incidence pattern and risk factor profile strongly suggest that intense immune suppression may act as a tumor promoter in high-risk individuals. These findings have implications for reducing melanoma risk in these and other patients undergoing intense iatrogenic immunosuppression.

Prior population-based studies of organ transplant recipients identified only 1 to 20 incident cutaneous melanomas each (16-22), and none examined melanoma incidence across periods of renal transplant function and failure. The incidence pattern that we observed suggests a strong effect of current immunosuppression, and an effect that is reversible upon cessation of immunosuppression. It is likely that heightened surveillance for nonmelanocytic skin cancer (NMSC) during periods of transplant function contributed to the relative deficit of melanoma diagnoses during periods of transplant failure. However, our interpretation is supported by a case report of clinical and dermatoscopic fading of melanocytic nevi after transplant failure and removal of immunosuppression (23). Our study reports the first population-based data that the effect of immune suppression on melanoma risk is reversible. As transmission of melanoma from donor to recipient is rare (estimated at 0.2% of incident cancers; ref. 24), this would have had very little effect on the incidence pattern observed.

Previous studies did not examine direct measures of immune suppression as a risk factor for melanoma, but in one study a history of at least one acute rejection episode was associated with melanoma risk (25). Our findings of a positive association with receipt of antibody and an inverse association with increasing time since transplantation suggest an association with the intensity of immune suppression, specifically the severity of T-cell depletion. Antibody therapy results in rapid and strong T-cell depletion, with CD4 cell depletion greatest within the first 3 months of receipt and gradual restoration over 5 to 10 years after polyclonal therapy (26, 27). In the United States Renal Data System cohort, melanoma risk was highest in older white males, supporting a role for UV radiation exposure and sensitivity (25). The importance of UV radiation exposure may explain the lack of an excess risk of cutaneous melanoma in transplant recipients in most (17-22), but not all (16), northern European countries. Not only are these settings with low ambient solar UVR, but in contrast to Australia prior to 1990 and the United States, induction antibodies are used less frequently for solid organ transplant recipients in these countries (22). On the other hand, the northern European studies examined smaller cohorts (n = 1,125-5,931), and

may have had insufficient statistical power to detect the modest overall increased risk we observed.

Given the somewhat limited power of this study, our findings do not exclude the possibility of a direct oncogenic effect on melanoma risk by the immunosuppressive agents, in particular the antiproliferative agents. In support of a direct effect, azathioprine has been shown to sensitize DNA to UV A radiation, reducing the minimal erythemal dose in the skin cells of treated patients (28, 29), and we have recently shown azathioprine to be a risk factor for squamous cell carcinoma of the lip in observational data from the same cohort (12). However, there is as yet no molecular evidence of a UV-related mechanism of mutagenesis for mycophenolate. Cyclosporine inhibits DNA repair and apoptosis in UV B radiation–exposed human keratinocytes (30, 31), yet this mechanism is believed to involve mutations in the *p53* tumor suppressor gene (32), which is common in NMSC but not in melanoma (33). Associations of melanoma risk with individual immunosuppressive agents or regimens are best examined in pooled, prospective randomized clinical trials.

Our data showing a peak in the relative risk of melanoma two years after transplantation, and a linear decline thereafter, suggest that immunosuppression may act as a tumor promoter in high-risk individuals with preneoplastic lesions prior to transplantation. Under such a scenario, the suppression of immune surveillance may facilitate or accelerate the proliferation of these cells in individuals with specific prior exposures and host characteristics, including genetic susceptibility. Such a mechanism was proposed on the basis of histopathologic evidence of a precursor nevus in all 10 evaluable primary tumors from an international case series of melanomas arising in transplant recipients (4), a finding that has not been replicated in two recent, small case series (34, 35). This observation and hypothesis is supported by case reports of eruptive melanocytic nevi shortly after the onset of immunosuppression, whether it be iatrogenic (7, 36, 37), HIV-related (8, 38), or chemotherapy-related (6, 9, 39).

The peak in melanoma risk in the second year post-transplantation may also reflect an association with the recency and rate of acquisition of immunosuppression, being rapid at the time of transplantation. Such an association could account for the steady return to baseline risk beyond the second year, and may also explain why people who acquire immune suppression gradually, such as those with HIV infection, are not at such heightened risk for melanoma (5, 40). It is also possible that the decline in risk beyond the second year may have been influenced by low ongoing UV radiation exposure in this group of patients who are counseled to avoid sun exposure because of their exceptionally high risk of NMSC.

Another explanation for the relationship of current immune suppression with melanoma risk could be that this cancer may be associated with an oncogenic virus. The potential role of infection by human papillomavirus (HPV) in the etiology of cutaneous melanoma is controversial, with most (41) but not all (42) investigations unable to detect HPV DNA in melanoma tissue. Given the high prevalence of HPV infection in immunosuppressed transplant recipients (43), a role for HPV in the genesis of melanoma is not excluded by our data. However, the decline in risk of melanoma with increasing duration of immunosuppression, a pattern that is opposite that for NMSC (20) and lip cancer (12), two cancers with a putative association with HPV, does not seem to support such an association.

The central strengths of this study include the population-based design, the size of the cohort, and the length of follow-up. ANZDATA registrants are actively followed

Table 3. Risk factors for cutaneous melanoma during the first functioning kidney transplant

	Person-years*	*n*	Univariate		Multivariate†	
			IRR (95% CI)	Overall *P*‡	IRR (95% CI)	Overall *P*‡
Age (single years)‡	47,778	74	1.04 (1.02-1.06)	<0.001	1.05 (1.03-1.07)	<0.001
Sex						
Males	28,125	52	1.00		1.00	
Females	19,653	22	0.61 (0.37-0.997)	0.049	0.57 (0.35-0.94)	0.028
Race						
Caucasoid	43,317	73	1.00		1.00	
Non-caucasoid	4461	1	0.13 (0.02-0.96)	0.043	0.15 (0.02-1.05)	0.056
Time since transplantation (y)§						
<5	27,033	46	1.00		1.00	
5-10	13,855	21	0.89 (0.53-1.49)		0.77 (0.45-1.29)	
≥10	6,890	7	0.60 (0.27-1.32)	0.215‖	0.47 (0.21-1.09)	0.063‖
Receipt of antiproliferative§						
No	6,725	19	1.00		1.00	
Yes	41,053	55	1.86 (0.81-4.28)	0.146	2.16 (0.93-5.03)	0.075
Receipt of calcineurin inhibitor§						
No	10,337	61	1.00		1.00	
Yes	37,441	13	1.43 (0.77-2.65)	0.260	1.42 (0.75-2.71)	0.282
Receipt of lymphocyte-depleting antibody§						
No	37,083	51	1.00		1.00	
Yes	10,694	23	1.56 (0.96-2.56)	0.075	1.73 (1.05-2.84)	0.030

*Person-years during first functioning transplant.
†Adjusted for current age (single years), sex, race, time since transplantation, receipt of immunosuppressive agents, and receipt of T lymphocyte-depleting antibody.
‡*P* values reported for test of homogeneity.
§Time-dependent; receipt of T lymphocyte-depleting antibody "Yes" from time of first receipt.
‖*P* value reported for test for trend.

up to identify all periods of renal replacement therapy, including dialysis, transplantation, redialysis, and retransplantation, enabling a within-cohort comparison of melanoma incidence. We believe this feature is globally unique to the ANZDATA Registry. Losses to follow-up in ANZDATA are <1% (44). Furthermore, cancer registration in Australia is mandated, and the completeness and accuracy of diagnoses are of high quality (45). Thus, the ascertainment of melanoma diagnoses was population-based, and patients were under follow-up for cancer until they emigrated from Australia. Cancer ascertainment was also reliant on data linkage, and the methodology we employed followed that used previously in identifying AIDS-related non-Hodgkin lymphoma in the New South Wales Cancer Registry, which was 99% sensitive and 100% specific (46). Thus, misclassification error is expected to be small.

Our study also had some limitations. Although the risk factor analyses were adjusted by age, sex, and race, information on other established risk factors for melanoma in the immune-competent, such as personal sun exposure, nevus count, ability to tan, melanoma susceptibility genes, and family history of cutaneous melanoma, were not available. Our lack of control for these factors may have biased some of the estimated effects we observed, although this would not affect the analysis of reversal of increased risk on reduction of immune suppression. In addition, we could not ascertain the occurrence of *in situ* melanomas in our cohort, and it is possible that heightened surveillance for NMSC led to the early diagnosis of such lesions and the avoidance of invasive melanoma in some patients.

These data provide an evidence base on which to minimize the risk of cutaneous melanoma in prospective and current kidney transplant recipients. Our findings also suggest that other patients in high–solar UVR settings with severe immune dysfunction are likely to be at increased risk of cutaneous melanoma. These patients include other solid organ transplant recipients, hematopoietic stem cell transplant recipients, HIV patients with very low CD4 counts, and patients with primary immunodeficiency disorders involving T-cell dysfunction. The excess risk may also extend to patients receiving immune-modifying agents for other conditions. Indeed, an increased incidence of melanoma has recently been observed in rheumatoid arthritis patients treated with methotrexate (47, 48). Although immune dysregulation related to the rheumatoid arthritis may have played a role in this finding, an elevated incidence of melanoma was not observed in large-scale population-based studies of rheumatoid arthritis patients prior to the use of such agents (49, 50).

In conclusion, this population-based study in a high–solar UV radiation setting suggests that the incidence of melanoma is closely related to current immune suppression. Opposite the pattern of overall cancer incidence after transplantation, and the incidence of NMSC, risk decreased with increasing duration of immune suppression. The possibility that intense iatrogenic immunosuppression acts as a tumor promoter for this cancer supports the need for frequent skin examinations to facilitate the early detection of malignant change in individuals at high risk of melanoma.

Disclosure of Potential Conflicts of Interest

Professor Chapman is on the advisory boards and speaker panels of Astellas, Novartis, Wyeth and Hoffmann la Roche, and he has received research support from the Juvenile Diabetes Foundation International, Novartis, Wyeth, Jannsen-Cilag, and Hoffmann la Roche. Professor Grulich is on the advisory board for the Gardasil human papillomavirus vaccine for the Commonwealth Serum Laboratories. No other authors reported financial disclosures.

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