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Risk of malignancy with long-term immunosuppression in renal transplant recipients

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Risk of malignancy with long-term immunosuppression in renal transplant recipients.

Background. Improvements in immunosuppressive regimens have significantly enhanced patient and graft survival in renal transplant recipients. However, susceptibility to neoplastic disorders is increased as a consequence of prolonged immunosuppression. Available data pertaining to cancer risks in renal transplant recipients have been inconsistent, and much of it is derived from international studies, which may not be truly representative of the United States population.

Methods. We studied a total of 1979 transplants performed in 1739 patients from a single center in the United States with a mean follow-up of 6.1 years, and a total of 9852 person-years' follow-up.

Results. The mean age at the time of diagnosis of cancer was 50 years, and the mean interval between transplant and diagnosis of cancer was 95 months. Older patients receiving a transplant had a significantly higher risk for developing cancer as opposed to younger patients (RR 6.2 for >60 years compared with <40 years). When compared with the general population using data from the Surveillance, Epidemiology and End Results (SEER) registry, the overall risk for nonskin malignancies was modestly increased in our transplant recipients, with a standardized incidence ratio (SIR) of 1.4 ($P = 0.01$). When stratified by age groups, younger age at transplant (<40 years) had the highest SIR, at 2.3 ($P < 0.001$). Similarly, duration post-transplant >10 years had an SIR of 2.4 ($P < 0.001$).

Conclusion. We believe that this study is representative of the United States' renal transplant population, and highlights the need for reduced immunosuppression in the long-term and increased vigilance for cancers in younger patients receiving renal transplantation.

Improvements in immunosuppressive regimens and general care of the renal transplant recipient have led to significantly enhanced graft survival [1]. Despite the substantial benefits to mortality [2] and quality of life [3], the result is longer exposure to immunosuppressive agents. In addition to infections, this has been associated with an increased risk of a variety of malignancies [4]. Many appear to be associated with viral infection [5], such as lymphomas (Epstein-Barr virus), cervical cancer (human papilloma virus), and Kaposi's sarcoma (human herpes virus 8). Others, such as acquired cystic disease and subsequent renal cell cancers [6], may be related to factors associated with a preceding period of uremia, or more generally, to a state of poor immune surveillance resulting from potent immunosuppressive medications [7].

One of the major repositories of information on malignancy after renal transplantation is from the very large Cincinnati Transplant Tumor Registry (CTTR), which represents a worldwide collection of cases [8]. However, it does not include information on person-years of follow-up, and therefore, cannot provide true estimates of cancer risk based on incidence. While a number of single-center and other registry studies have been published trying to address this limitation, few had long periods of follow-up or attempted to compare cancer risk with the general population [9–18]. Furthermore, most studies are internationally based, and therefore may not be representative of the United States (U.S.) population because it is known that the frequency and type of malignancies vary significantly depending on the population studied [5, 8].

We studied a large group of renal transplant recipients from a single center in the U.S. over a 35-year time span to determine the incidence of malignancy compared with the general population.

Key words: kidney transplantation, imunosuppression, post-transplant neoplasms, cancer risk.

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METHODS

Patient population

This study was a retrospective review of data collected contemporaneously on all patients undergoing renal transplantation at the University of Texas Medical

Branch between July 1967 and May 2002. Although patients could receive transplant follow-up elsewhere, contact was usually maintained with the study center on at least an annual basis. Given the long period of study, immunosuppressive regimens employed varied considerably. Before 1984, the regimen primarily included dual therapy with azathioprine and prednisone. Since 1984, triple therapy with cyclosporine, azathioprine, and prednisone has been most commonly used. In 1997, mycophenolate mofetil replaced azathioprine as the third agent. Tacrolimus was introduced in 1996, and has been increasingly used in place of cyclosporine. Antibody agents have been used as induction therapy in patients deemed to be at high immunologic risk, and for delayed graft function. Rejection episodes were initially treated with pulse methylprednisolone. Steroid-resistant, or severe rejection, episodes were treated with the monoclonal antibody OKT3 or polyclonal antithymocyte globulin (ATG). Equine ATG was used until 1999, when it was replaced by a rabbit preparation. Monoclonal antibodies directed against the interleukin (IL)-2 receptor have also been used for induction since 1999. With the various regimens, 1-year graft survivals for primary cadaveric transplants have been 42%, 78%, and 91% for the periods before 1980, 1984 to 1989, and 1996 to 1998, respectively.

The study protocol was approved by the local Institutional Review Board of the University of Texas Medical Branch.

Data collection

Information for the study population was primarily obtained from a computerized database maintained at the study center on all transplant patients. Data collected for this study included demographics such as age, gender, and race, as well as information on the etiology of end-stage renal disease (ESRD), donor source (living or cadaveric), occurrence of neoplasm, date of transplant, graft, and patient survival. For patients identified as having malignancy, medical records, when available, were reviewed to confirm the histology and date of diagnosis.

General population data on the incidence of malignancy were obtained from the Surveillance, Epidemiology and End-Results (SEER) registry [19]. The SEER program is sponsored by the National Cancer Institute and consists of a group of population-based tumor registries encompassing 11 states and covering approximately 14% of the U.S. population in its most recent form. Of note, it excludes nonmelanoma skin cancer cases, and current data spans from 1973 to 1999.

Statistical analysis

For purposes of the analyses and defining years of follow-up, patients were censored at the time of death, return to dialysis, diagnosis of malignancy, or at last time of contact with the study center. Kaplan-Meier curves were generated to estimate the cumulative probability of malignancy-free graft survival. Means were calculated ± standard deviation (SD).

To examine risk factors for the development of malignancy in renal transplantation, multivariable regression was performed using the Cox proportional hazards technique, with time to malignancy as the dependent variable. Potential risk factors entered as independent variables in the model were: age at transplant, race, transplant number, donor source, transplant year, and cause of ESRD. For transplant year, a cut-off of 1984 was used because this roughly separates the eras with and without calcineurin inhibitor use. Relative risks with 95% confidence intervals (CIs) were estimated for each risk factor. A P value < 0.05 was considered significant. A second model was created excluding nonmelanoma skin cancer cases to allow for comparability with the SEER general population data analyses.

To estimate risk compared with the general population, standardized incidence ratios (SIR) were calculated for nonskin cancers based on observed compared with expected numbers generated by multiplying the person-years at risk by the appropriate sex-, race-, age-, and calendar year–specific incidence rates obtained from publicly available SEER data [20]. Cancer cases occurring before 1973 or after 1999 were attributed to the years 1973 and 1999, respectively. SIRs were also calculated for a variety of strata, including age, race, selected sites of cancer, donor source, transplant number, transplant year, duration of post-transplant, and cause of ESRD. The majority of patients listed as Hispanic in the study center were Mexican-American. The SIR for Hispanic race was determined using the term "White Hispanic" in the SEER data and calculated only for cases since 1992, when the designation was introduced. Cases with incomplete follow-up data were excluded from analysis. A 95% CI was generated for each SIR assuming a Poisson distribution for the observed number of cases. A standard P value < 0.05 was used for statistical significance. However, given the possibility of chance findings with multiple testing, a more conservative significance level was also calculated using the Bonferroni adjustment.

All analyses were performed using SAS (version 8, Cary, NC, USA).

RESULTS

A total of 1979 transplants were performed in 1739 patients during the study period. This resulted in a total of 9852 person-years, with a mean follow-up of 6.1 years. Twenty-one percent of patients were followed for more than 10 years' post-transplantation, with the longest follow-up being 30.3 years. Clinical and demographic

Table 1. Patient and transplant characteristics

	Cancer	All transplants
Patient characteristic		
Total patients	92	1739
Gender		
Female	32 (34.8%)	687 (39.5%)
Male	60 (65.2%)	1052 (60.5%)
Race		
Caucasian	53 (57.6%)	886 (50.9%)
African American	18 (19.6%)	376 (21.6%)
Hispanic	21 (22.8%)	449 (25.8%)
Others	0	28 (1.6%)
Cause of ESRD		
DM	11 (12.0%)	362 (20.8%)
HTN	25 (27.2%)	315 (18.1%)
Glomerulonephritis	19 (20.7%)	309 (17.8%)
Miscellaneous[a]	37 (40.2%)	753 (43.3%)
Transplant characteristics		
Total transplants	92	1979
Age at transplant *years*		
<40	34 (37.0%)	1102 (55.6%)
40 to 59	48 (52.2%)	749 (37.9%)
≥60	10 (10.9%)	128 (6.5%)
Mean age at transplant (years) ± SD	43.5 ± 13.5	36.4± 15.8
Number of transplants		
1	76 (82.6%)	1739 (87.9%)
2	14 (15.2%)	213 (10.8%)
≥3	2 (2.2%)	27 (1.4%)
Donor source		
Cadaveric	76 (82.6%)	1504 (76.0%)
Living related	14 (15.2%)	447 (22.6%)
Living unrelated	2 (2.2%)	28 (1.4%)
Transplant year		
<1984	26 (28.3%)	520 (26.3%)
≥1984	66 (71.7%)	1459 (73.7%)

Abbreviations are: DM, diabetes mellitus; HTN, hypertension.
[a]Including renal dysplasia/agenesis, Alport's disease, chronic pyelonephritis, autosomal-dominant polycystic kidney disease, and etiology unknown.

Table 2. Types of malignancy

Category	Type	Frequency
Skin	Squamous cell carcinoma	18
	Basal cell carcinoma	8
	Both basal and squamous	7
	Melanoma	2
	Unspecified	2
	Total	37
Gastrointestinal	Colorectal	6
	Esophageal	3
	Cholangiocarcinoma	1
	Hepatoblastoma	1
	Hepatocellular carcinoma	1
	Total	12
Urologic	Renal cell carcinoma	6
	Transitional cell carcinoma	3
	Wilm's tumor	1
	Total	10
Genital	Cervical carcinoma	2
	Vulvar carcinoma	1
	Total	3
Breast	Total	4
Lung	Total	4
Lymphomas	Total	8
Kaposi's sarcoma	Total	2
Prostate	Total	2
Thyroid	Total	1
Others[a]	Total	9
Total	Total	92

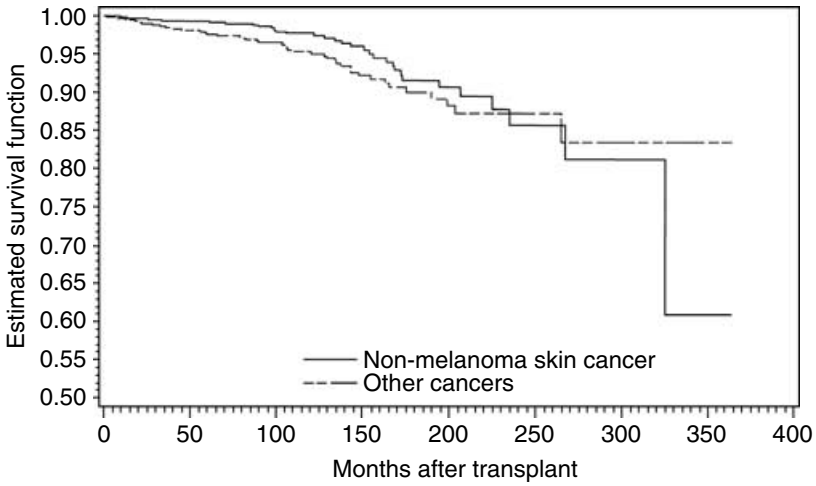
[a]Unknown primary (3), sarcoma (2), unspecified type (1), oligodendroglioma (1), mucoepidermoid carcinoma (1), myelofibrosis (1).

characteristics of patients and transplants with and without cancer is shown in Table 1. Most patients were male, had a cadaveric donor, and were transplanted after 1984. Patients were racially diverse, with roughly half being Caucasian, and the remainder divided between African-American and Hispanic groups. The distributions for most characteristics were generally similar between patients with and without cancer, with the exception of age. Patients with cancer appeared to be older at the time of transplant, with a mean age of 43.5 years compared with 36.4 years for those without cancer.

A total of 92 cancers were identified, with a mean time between transplant and diagnosis of 95 ± 71 months (range 1.3 to 325). The mean age at time of diagnosis was 50 ± 12 years. Fifty-four (59%) cases received antibody induction. Table 2 lists the types of malignancy observed. Skin cancer was most common, representing 40% of the neoplasms diagnosed. The next most common sites were gastrointestinal (13%), urologic (11%), and lymphomas (9%). Figure 1 shows a Kaplan-Meier curve of malignancy-free survival. The long-term cumulative incidence was 19% for nonmelanoma skin cancer, and 17% for other cancers, yielding a total incidence of malignancy of 36% at 25 years.

Table 3 presents two multivariable models examining risk factors for development of malignancy after renal transplantation, both including and excluding nonmelanoma skin cancer. For both models, the only factor to achieve statistical significance was age at transplantation. This demonstrated increasing risk of malignancy with older age.

Table 4 exhibits standardized incidence ratios comparing the renal transplant cohort with the general population for the different demographic and clinical characteristics for only those patients with nonskin cancers. Using a P value < 0.05 as a cut-off, the SIR for all cancers was significant at 1.4. For individual sites of malignancy, breast and lung cancer appeared less frequently in the transplant population, with a SIR of 0.7 each, while lymphomas, renal cancers, and colorectal cancers were more common in transplanted patients, with SIRs of 4.9, 7.2, and 1.5, respectively. Only the youngest age category of less than 40 years at the time of transplantation had a significantly elevated SIR at 2.3. Hispanic and African American race, two or more transplants, living donor, hypertension as cause of ESRD, and duration of post-transplant >10 years all had significantly elevated SIRs. Using the more conservative Bonferroni corrected P value of 0.002, only age <40 years, lymphomas, renal cell cancers, two or more transplant number, and post-transplant duration >10 years remained significant.



Number of evaluable patients	0 years	5 years	10 years	15 years	20 years	25 years
Non-melanoma skin cancer	1637	888	401	149	42	18
Other cancers	1637	789	332	141	85	22

Fig. 1. Kaplan-Meier curve of malignancy-free survival.

DISCUSSION

This is the first single-center study from a U.S.-based renal transplant program that provides cancer risk estimates in comparison to the general population. It not only confirms, but extends, the results of previous studies addressing the issue of malignancy after renal transplantation.

The overall risk of cancer in renal transplant recipients in our study was only slightly increased, with a SIR of 1.4 ($P = 0.01$). This is in contrast to other studies, which found higher overall risks ranging from 3.3 to 3.6 [10, 21]. However, these were primarily driven by the high frequency and particularly elevated risk for skin cancers, which were excluded from our analysis. As discussed further below, it appears that specific subsets of cancers and patient or transplant characteristics are associated with a particularly elevated risk for malignancy compared with the general population.

First, consistent with the pattern observed in the general population and as demonstrated in previous reports [14], it appears that older patients have a greater risk for developing malignancy after transplantation (RR 6.2 for age ≥60 compared with <40 years). However, it is noteworthy that the youngest group at the time of transplantation has the highest relative risk compared with the age-matched general population, with a SIR of 2.3. This finding has not been addressed extensively in previous studies, although it is noted on examination of data presented in some [10, 15]. It is also consistent with the pattern observed in the very large collaborative study of cancer risk in chronic dialysis patients [22]. One possible explanation is that patients transplanted at a younger age have a longer life expectancy post-transplant, and may therefore have a particularly increased exposure to the risks of immunosuppression. Second, younger patients may not have been exposed to certain viruses until after transplantation, possibly increasing the risk of virus-related malignancy. An example of this is post-transplant lymphoma, which is most likely to occur in patients who are Epstein-Barr virus–seronegative before transplantation [23]. In summary, this issue is especially important because cancer in younger patients may result in a greater potential of years of life lost, and raises the question of whether this group requires increased cancer surveillance post-transplantation.

There is ongoing controversy over the primary mechanisms of cancer risk in the setting of immunosuppression [7]. One hypothesis is that cancers result from oncogenic viral infections that are no longer kept in check by the depressed immune system. The data from the CTTR supports this contention because its main findings primarily demonstrate an increase in those malignancies with a clear association with viral infection, such as lymphomas, cervical cancer, and Kaposi's sarcoma [8]. The other proposed mechanism is that of reduced immune surveillance against a variety of nonviral tumor antigens [24]. Data consistent with this comes from both the Nordic [20] and Australia/New Zealand [25] renal transplant registries, which show a more widespread increase in all kinds of malignancies, including the common solid organ cancers seen in the general population, with the exception of breast cancer. Our data provides support for both of these mechanisms. Consistent with findings of almost all studies examining post-transplant malignancy, we found an increase in the risk for lymphoma, which is commonly associated with Epstein-Barr virus infection.

Table 3. Risk factors for malignancy post renal transplantation: Multivariable analyses

Characteristic	All cancers		Excluding nonmelanoma skin cancer	
	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Age at first transplant *years*				
<40 – reference	1.0	<0.001	1.0	<0.001
40 to 59	2.9 (1.8, 4.6)		3.6 (1.9, 6.7)	
≥60	6.2 (2.8, 13.5)		6.6 (2.5, 17.1)	
Race				
Caucasian/Other – reference	1.0	0.389	1.0	0.469
African American	0.7 (0.4, 1.3)		1.5 (0.8, 3.0)	
Hispanic	0.7 (0.5, 1.3)		1.3 (0.7, 2.5)	
Number of transplants				
1 – reference	1.0	0.757	1.0	0.350
≥2	1.1 (0.6, 2.0)		1.5 (0.7, 3.2)	
Donor source				
Living – reference	1.0	0.682	1.0	0.989
Cadaveric	1.1 (0.7, 1.8)		1.1 (0.7, 1.8)	
Transplant year				
<1984 – reference	1.0	0.800	1.0	0.418
≥1984	1.1 (0.6, 1.8)		1.3 (0.7, 2.7)	
Cause of ESRD				
DM – reference	1.0	0.471	1.0	0.230
HTN	1.6 (0.8, 3.4)		2.3 (0.9, 6.0)	
Glomerulonephritis	1.0 (0.5, 2.3)		1.3 (0.5, 3.8)	
Miscellaneous	1.1 (0.6, 2.3)		1.5 (0.6, 4.0)	

Table 4. Standardized incidence ratios

Characteristic	Cancer patients	*N*[a]	Person-years	SIR (95% CI)	*P* value
All cancers	57	1637	9852	1.4 (1.1, 1.8)	0.010
Site of cancer					
Breast	4	1637	9959	0.7 (0.5, 0.9)	0.005
Lung	4	1637	9955	0.7 (0.5, 0.9)	0.023
Colorectal	6	1637	9956	1.5 (1.1, 1.9)	0.007
Renal cell	6	1637	9941	7.2 (2.8, 18.7)	<0.001
Lymphomas	8	1637	9946	4.9 (2.1, 11.2)	<0.001
Age at transplant *years*					
<40	18	864	6076	2.3 (1.7, 3.1)	<0.001
40 to 59	32	675	3322	1.3 (0.9, 1.9)	0.103
≥60	7	123	454	0.8 (0.5, 1.2)	0.265
Race					
Caucasian	23	831	5163	1.1 (0.8, 1.4)	0.639
African-American	18	354	1941	1.6 (1.2, 2.3)	0.006
Hispanic	5	207	732	2.4 (1.3, 4.5)	0.008
Number of transplants					
1	48	1637	8853	1.3 (1.0, 1.6)	0.072
≥2	9	183	1000	2.9 (1.7, 4.9)	<0.001
Donor source					
Cadaveric	43	1287	6765	1.3 (1.0, 1.8)	0.081
Living	14	427	3087	1.7 (1.1, 2.6)	0.026
Transplant year					
<1984	12	365	2836	1.4 (0.9, 2.2)	0.092
≥1984	45	1314	7016	1.4 (1.0, 1.9)	0.050
Duration post-transplant *years*					
≤5	27	1637	5668	1.2 (0.9, 1.6)	0.205
6 to 10	13	834	2588	1.1 (0.5, 2.6)	0.775
>10	17	355	1596	2.4 (1.6, 3.8)	<0.001
Cause of ESRD					
DM	6	355	1618	0.8 (0.5, 1.3)	0.419
HTN	21	307	1748	1.6 (1.2, 2.3)	0.002
Glomerulonephritis	10	290	2115	1.2 (0.9, 1.7)	0.255
Miscellaneous	20	685	4371	1.5 (0.9, 2.5)	0.099

[a]102 cases with missing follow-up data were excluded.

Breast and lung cancers, on the other hand, appeared to have a slightly lower risk compared with the general population. This finding is consistent with previous studies [26], including the CTTR. This could occur as a result of intense medical screening that is part of the evaluation process before transplantation, leading to the exclusion of high-risk patients. In contrast to the CTTR, we did observe an increase in colon cancers consistent with the

reduced immune surveillance hypothesis. This has also been demonstrated in previous studies, particularly in those with long periods of follow-up such as ours [10, 12]. One such study found that the risk for colon cancer increased only after 10 years post-transplantation [12]. We also observed that the risk for renal cell cancer was substantially increased, over 7-fold higher than in the general population. However, it is unclear whether the risk for renal cell carcinoma is influenced by immunosuppression because it is very difficult to control for the known risk related to a preceding period of uremia. We had no comparison group of patients on dialysis available to examine this issue. One study addressing this issue showed no further increase in risk of renal cancer in transplant patients compared with those on dialysis [12]. However, it may still be prudent to strongly consider surveillance for renal cell cancer with ultrasound or computed tomography, as has been suggested previously [6]. In summary, we have demonstrated an increase in certain cancers with and without clear viral associations, supporting a role for both proposed mechanisms for carcinogenesis after transplant immunosuppression.

It is intuitive that an increase in the amount of immunosuppression may lead to a greater risk of malignancy. This has been shown previously with use of more intense immunosuppressive regimens, correlating with the occurrence of post-transplant lymphoma [27] and a longer duration of immunosuppression, correlating with subsequent development of skin cancers [28]. Our data also support this principle in a number of ways. Both a higher transplant number and longer duration post-transplant were very strongly associated with an increased risk of cancer compared with the general population. In addition, although limited by power, we were unable to demonstrate a difference in cancer risk between the two eras of immunosuppression. Although data is conflicting, other studies have similarly found no difference in malignancy risk when comparing primarily azathioprine- versus cyclosporine-based regimens [24, 29, 30]. Overall, this strongly suggests that the duration and possibly total dose of immunosuppression, rather than the type of immunosuppression, is the most important factor in the subsequent development of malignancy. Of note, the incidence of malignancy in our study (skin included) approaches almost 40% after 25 years of transplantation. This correlates well with figures ranging from 17% to 50% at 20 years from various previous studies with long-term follow-up [10, 14, 29].

No increased risk was detected among racial groups for patients undergoing transplantation, although the analysis was limited by small numbers. Of potential interest was that among the racial groups, the risk of cancer compared with the general population was highest for the transplanted Hispanic group, with an SIR of 2.4. Although this could be a chance finding, it is noteworthy that the Hispanic general population demonstrates a lower incidence of malignancy compared with Caucasians [31]. A potential explanation for this is that Hispanics either have less access to, or are less likely to, seek access to health care. The issue of access to care may be obviated in transplanted patients, which out of necessity receive frequent medical follow-up, resulting in an exaggerated increase in cancer incidence in the transplanted Hispanic group not present in Caucasians when a comparison is made to the general population.

There are several limitations to this study, most of which relate to its single-center nature. Even with the long time span, the total number of cancers was small relative to much larger registry studies, thus substantially limiting the power to detect weak associations. In addition, stratification into multiple subgroups increases the risk of chance findings. We attempted to limit this by employing a Bonferroni corrected P value in order to provide a more conservative measure, of which findings were most likely to be valid. However, we still presented data with a standard P value of 0.05 as well so as not to dismiss weaker but potentially important findings. Advantages of this study include the ability to produce true cancer risk estimates on the basis of incidence as calculated by person-years, which are not available from a large registry such as the CTTR. The utilization of the SIR, which incorporates the duration of follow-up available, minimizes problems with loss to follow-up which can substantially affect cancer risks based purely on a percentage of cases of cancer seen, rather than incidence based on person-years. However, we cannot exclude the possibility that some patients were lost to follow-up *because* they died from malignancy, which would tend to lead to an underestimation of the cancer risks we have presented. Finally, the long period of follow-up available for many patients allowed estimation of cancer risk in the long-term.

CONCLUSION

This study provides cancer risk estimates after renal transplantation compared with the U.S. general population data available from SEER. Its results emphasize the need for vigilance after transplantation given the findings of a heightened risk of a variety of malignancies, particularly affecting the younger age groups, and with a progressive increase in incidence over the duration of the transplant. This highlights the need for strategies to limit the amount of immunosuppression given in the long-term to prevent the many successes of transplantation being marred by the risk of malignancy.

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