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Effect of reduced immunosuppression after kidney transplant failure on risk of cancer: population based retrospective cohort study

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ABSTRACT

Objective To compare cancer incidence in kidney transplant recipients during periods of transplant function (and immunosuppression) and after transplant failure (when immunosuppression is ceased or reduced).

Design, setting, and participants Nationwide, population based retrospective cohort study of 8173 Australian kidney transplant recipients registered on the Australia and New Zealand Dialysis and Transplant Registry who first received a transplant during 1982-2003. Incident cancers were ascertained using linkage with national cancer registry records.

Main outcome measures Cancer-specific standardised incidence ratios for periods of transplant function and for dialysis after transplant failure. Incidence was compared between periods using multivariate incidence rate ratios adjusted for current age, sex, and duration of transplantation.

Results All cases of Kaposi's sarcoma occurred during transplant function. Standardised incidence ratios were significantly elevated during transplant function, but not during dialysis after transplant failure, for non-Hodgkin's lymphoma, lip cancer, and melanoma. For each of these cancers, incidence was significantly lower during dialysis after transplant failure in multivariate analysis (incidence rate ratios 0.20 (95% CI 0.06 to 0.65) for non-Hodgkin's lymphoma, 0.04 (0.01 to 0.31) for lip cancer, and 0.16 (0.04 to 0.64) for melanoma). In contrast, standardised incidence ratios during dialysis after transplant failure remained significantly elevated for leukaemia and lung cancer, and cancers related to end stage kidney disease (kidney, urinary tract, and thyroid cancers), with thyroid cancer incidence significantly higher during dialysis after transplant failure (incidence rate ratio 6.77 (2.64 to 17.39)). There was no significant difference in incidence by transplant function for other cancers.

Conclusions The effect of immunosuppression on cancer risk is rapidly reversible for some, but not all, cancer types. Risk reversal was mainly observed for cancers with a confirmed infectious cause. Risk of other cancers, especially those related to end stage kidney disease, remained significantly increased after reduction of immunosuppression.

INTRODUCTION

A broad range of cancers, particularly those related to infection, occur at excess rates after solid organ transplantation—a situation similar to that seen in HIV infection.[1] In HIV infection, the partial reversal of immunodeficiency that is associated with antiretroviral therapy rapidly and substantially reduces the risk of Kaposi's sarcoma[2] and non-Hodgkin's lymphoma.[3] There are few data on whether the risk of other cancers is also reduced.[4-6] In transplant recipients, clinical regression of cases of Kaposi's sarcoma[7 8] and non-Hodgkin's lymphoma[9 10] has been described after reduction of iatrogenic immunosuppression. However, as in HIV infection, there are few data on whether cancer risk is reduced when immunosuppression is ceased.

In kidney transplant recipients, transplant failure generally leads to the reinstitution of dialysis and the substantial reduction or complete withdrawal of immunosuppression.[11] This offers a unique opportunity to examine the cancer risk profile on reduction of immunosuppression.[12] Recently, we showed that incidence of lip cancer,[13] non-Hodgkin's lymphoma,[14] and melanoma[15] decreased markedly after kidney transplant failure and reinstitution of dialysis. In the present paper, we report on the site-specific pattern of cancer occurrence during periods of transplant function and during periods of dialysis after transplant failure in an Australian cohort of kidney transplant recipients.

METHODS

Data sources

The Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry is a comprehensive, population based registry of all patients commencing maintenance dialysis or undergoing kidney

transplantation in Australia and New Zealand.[16] Our study cohort included all patients on the ANZDATA Registry in Australia who first received a transplant between 1 January 1982 and 30 September 2003 (n=8173). Incident cancers were ascertained through probabilistic record linkage with the Australian National Cancer Statistics Clearing House, which contains data on all diagnoses of incident invasive cancer in Australia since 1982, with the exception of non-melanoma skin cancer.[17]

For each matched record, we obtained the date of cancer diagnosis and ICDO-3 and ICD-10 (international classifications of diseases) codes for topography and morphology.[18] We also obtained the general population's cancer incidence rates by five year age group, sex, calendar year, and state or territory, for each year since 1982. Data were available to 2001, 2002, or 2003 depending on jurisdiction of cancer registration.

Statistical analysis

Person years of follow-up were accumulated from the date of first transplantation until the date of death, last contact, the latest date for which cancer data were available, or the first diagnosis of each type of cancer. Cancer incidence was examined during periods of transplant function and of dialysis after transplant failure. Person years and incident cancers during the first three months of each period were excluded, as cancers diagnosed within this time would almost certainly have developed in the preceding period.

For each period, we calculated cancer-specific standardised incidence ratios (with 95% confidence intervals) by comparing the number of observed cases with that expected based on the application of the appropriate population cancer incidence rates.[19] The exception was for Kaposi's sarcoma, in which we applied population rates from 1982 because of the impact of AIDS related Kaposi's sarcoma in the years thereafter.

Comparison of period-specific standardised incidence ratios may be confounded by differences in the age and sex structure of the cohort over time. Therefore, for each cancer, we used multivariate Poisson regression to compute incidence rate ratios with 95% confidence intervals comparing incidence during each period, with adjustment for current age (time dependent, single years), sex, and the cumulative duration of transplant function (time dependent, years). For cancers with zero cases during dialysis, we calculated a median unbiased estimate of the incidence rate ratio using exact Poisson regression adjusted for current age (time dependent, <35, 35-50, ≥50 years), sex, and duration of transplant function (time dependent, <2, 2-4.99, 5-9.99, 10-14.99, ≥15 years).[20]

A two sided P value of <0.05 was considered statistically significant. All analyses were performed using Stata version 10 (StataCorp, College Station, TX, USA).

Grouping of cancers

Analyses were restricted to cancers or groups of cancers (anogenital, oral cavity, and oropharyngeal cancers) for which there were at least 10 cases in total. For descriptive purposes, cancers were grouped according to their association with infection, end stage kidney disease, or immunodeficiency. Cancers associated with infection were those for which there is sufficient evidence of causality according to the International Agency for Research on Cancer.[21] These included Kaposi's sarcoma (human herpesvirus type 8); immunosuppression related non-Hodgkin's lymphoma and Hodgkin's lymphoma (Epstein-Barr virus); anogenital, oropharyngeal, and oral cavity cancers (human papillomavirus); liver cancer (hepatitis B virus and hepatitis C virus); and cancer of the stomach (*Helicobacter pylori*).
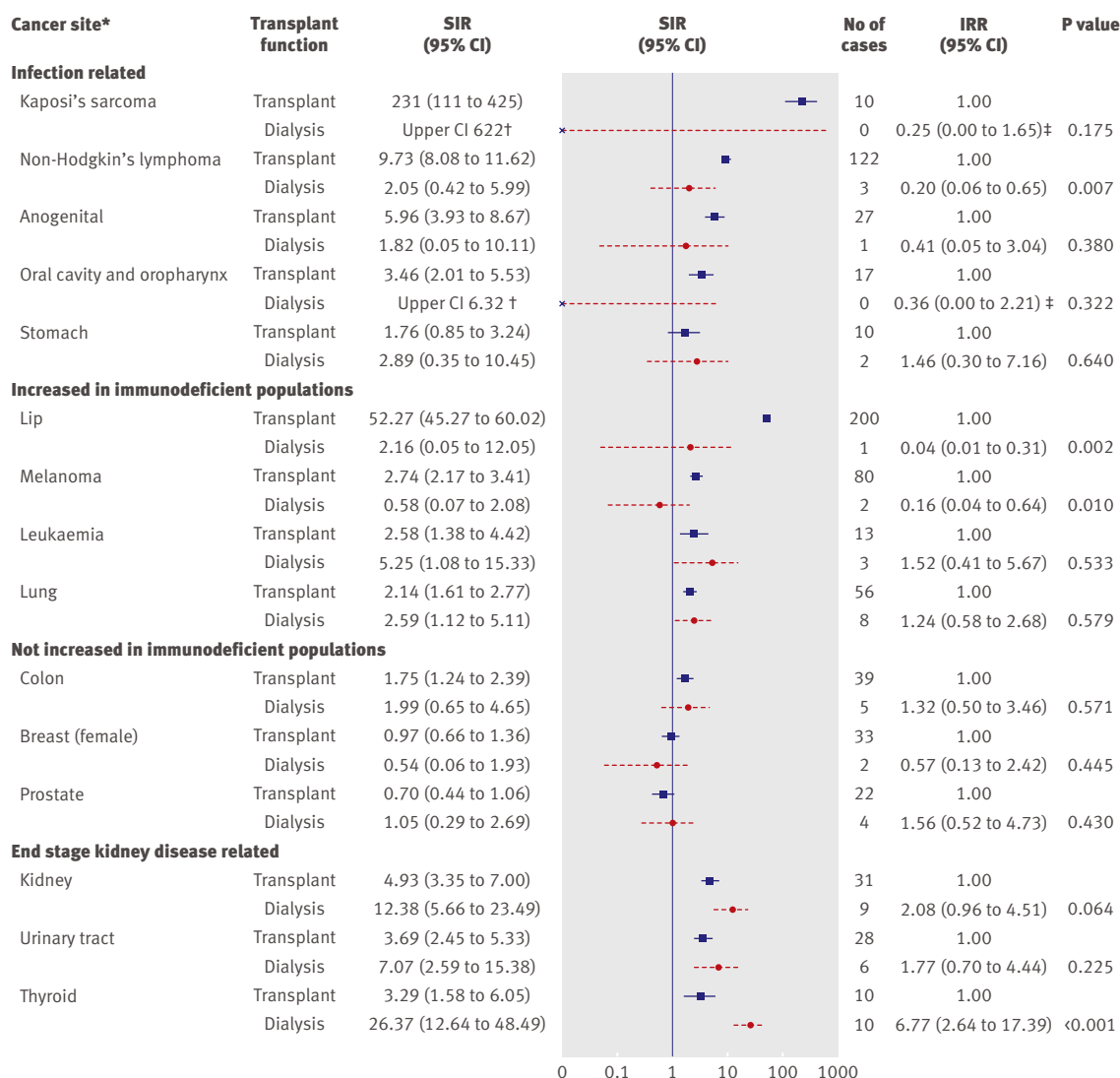
Cancers associated with end stage kidney disease (cancers of the kidney, urinary tract, and thyroid) were those for which our group had previously shown the relative risk to be at least doubled before renal replacement therapy,[18] and for which there is no, or a much smaller, excess risk in people infected with HIV.[1] Remaining cancers were grouped according to their association with immunodeficiency, based on whether they occur at increased rates after both solid organ transplantation and HIV infection according to meta-data.[1]

RESULTS

The study cohort comprised 7809 patients (4628 males, 3181 females), 364 patients having been censored because of exclusion of follow-up during the first three months of each period. In total, 925 cancers were identified; 33 (3.4%) of these were excluded because they occurred in the first three months of the transplant (n=11) or dialysis (n=22) period. This left 892 cancers identified over 59037 person years. The median age of patients at first transplantation was 43 years. Failure of the first transplant necessitating institution of dialysis occurred in 1820 (23%) patients, and 668 (9%) underwent a second transplantation. Three or more transplants were received by 66 (1%) patients. In total, there were 51933 person years (mean 6.9) during periods of transplantation and 7104 person years (mean 3.9) during dialysis after transplant failure.

Incidence of cancer by transplant function

The figure shows the cancer-specific standardised incidence ratios for the periods of transplant function and dialysis after transplant failure standardised by five year age group, sex, state or territory, and calendar year. It also shows the multivariate incidence rate ratios comparing incidence during dialysis after transplant failure with that during transplant function, adjusted for current age, sex, and cumulative duration of transplant function.

Cancer site*	Transplant function	SIR (95% CI)	SIR (95% CI)	No of cases	IRR (95% CI)	P value
Infection related						
Kaposi's sarcoma	Transplant	231 (111 to 425)		10	1.00	
	Dialysis	Upper CI 622†		0	0.25 (0.00 to 1.65)‡	0.175
Non-Hodgkin's lymphoma	Transplant	9.73 (8.08 to 11.62)		122	1.00	
	Dialysis	2.05 (0.42 to 5.99)		3	0.20 (0.06 to 0.65)	0.007
Anogenital	Transplant	5.96 (3.93 to 8.67)		27	1.00	
	Dialysis	1.82 (0.05 to 10.11)		1	0.41 (0.05 to 3.04)	0.380
Oral cavity and oropharynx	Transplant	3.46 (2.01 to 5.53)		17	1.00	
	Dialysis	Upper CI 6.32 †		0	0.36 (0.00 to 2.21) ‡	0.322
Stomach	Transplant	1.76 (0.85 to 3.24)		10	1.00	
	Dialysis	2.89 (0.35 to 10.45)		2	1.46 (0.30 to 7.16)	0.640
Increased in immunodeficient populations						
Lip	Transplant	52.27 (45.27 to 60.02)		200	1.00	
	Dialysis	2.16 (0.05 to 12.05)		1	0.04 (0.01 to 0.31)	0.002
Melanoma	Transplant	2.74 (2.17 to 3.41)		80	1.00	
	Dialysis	0.58 (0.07 to 2.08)		2	0.16 (0.04 to 0.64)	0.010
Leukaemia	Transplant	2.58 (1.38 to 4.42)		13	1.00	
	Dialysis	5.25 (1.08 to 15.33)		3	1.52 (0.41 to 5.67)	0.533
Lung	Transplant	2.14 (1.61 to 2.77)		56	1.00	
	Dialysis	2.59 (1.12 to 5.11)		8	1.24 (0.58 to 2.68)	0.579
Not increased in immunodeficient populations						
Colon	Transplant	1.75 (1.24 to 2.39)		39	1.00	
	Dialysis	1.99 (0.65 to 4.65)		5	1.32 (0.50 to 3.46)	0.571
Breast (female)	Transplant	0.97 (0.66 to 1.36)		33	1.00	
	Dialysis	0.54 (0.06 to 1.93)		2	0.57 (0.13 to 2.42)	0.445
Prostate	Transplant	0.70 (0.44 to 1.06)		22	1.00	
	Dialysis	1.05 (0.29 to 2.69)		4	1.56 (0.52 to 4.73)	0.430
End stage kidney disease related						
Kidney	Transplant	4.93 (3.35 to 7.00)		31	1.00	
	Dialysis	12.38 (5.66 to 23.49)		9	2.08 (0.96 to 4.51)	0.064
Urinary tract	Transplant	3.69 (2.45 to 5.33)		28	1.00	
	Dialysis	7.07 (2.59 to 15.38)		6	1.77 (0.70 to 4.44)	0.225
Thyroid	Transplant	3.29 (1.58 to 6.05)		10	1.00	
	Dialysis	26.37 (12.64 to 48.49)		10	6.77 (2.64 to 17.39)	<0.001

0   0.1   1   10   100   1000

Cancer-specific standardised incidence ratios (SIR) by transplant function and multivariate incidence rate ratios (IRR). *ICDO-3 and ICD-10 codes for cancers: Kaposi's sarcoma (C46); non-Hodgkin's lymphoma (ICDO-3 9591, 9670-9729, 9820-9837, 9940, and 9948, and 9590 if ICD-10 C82-C85); anogenital (C21 anus, C51-53 vulva, vagina, cervix uteri, C60 penis); oropharyngeal and oral cavity (C01-C02 tongue, C03-C06 mouth, C09 tonsil, C10 oropharynx); stomach (C16); lip (C00); melanoma (C43); leukaemia (ICDO-3 9800-9989 excluding 9820-9837, 9940, and 9948); lung (C33-34); colon (C18); breast (C50); prostate (C61); kidney (C64); urinary tract (C65-C68); thyroid (C73). †Upper confidence interval presented when zero cases observed. ‡Median unbiased estimate.

Cancers related to infection

The standardised incidence ratio for Kaposi's sarcoma (10 cases) was substantially elevated during transplant function; multivariate analysis was not performed as no cases occurred during dialysis after transplant failure.

The standardised incidence ratio for non-Hodgkin's lymphoma was significantly elevated during transplant function, but not during dialysis after transplant failure. In the multivariate analysis with adjustment for current year of age, sex, and the cumulative duration of transplant function, cancer incidence was significantly lower during dialysis after transplant failure than during transplant function.

Standardised incidence ratios for cancers associated with human papillomavirus infection (anogenital, oral cavity, and oropharyngeal cancers) were significantly elevated during transplant function, but not during dialysis after transplant failure. In multivariate analysis, incidence was not significantly lower during dialysis after transplant failure, including when all the cancer sites associated with human papillomavirus were combined (incidence rate ratio 0.24 (95% confidence interval 0.03 to 1.74), P=0.157).

Standardised incidence ratios for stomach cancer were not significantly elevated, and there was no difference in incidence between periods in multivariate analysis.

There were insufficient cases of other infection related cancers, including Hodgkin's lymphoma (n=7) and liver cancer (n=4), for analysis.

Cancers related to end stage kidney disease

For cancers of the thyroid, kidney, and urinary tract, standardised incidence ratios were significantly elevated both during transplant function and dialysis after transplant failure. In multivariate analysis, incidence was significantly increased during dialysis after transplant failure for thyroid cancer and was non-significantly increased for cancer of the kidney. There was no difference in incidence between periods for cancers of the urinary tract.

Other cancers

Standardised incidence ratios were significantly elevated during transplant function, but not during subsequent dialysis, for lip cancer and melanoma. For both cancers, incidence was significantly lower during dialysis after transplant failure in multivariate analysis. Standardised incidence ratios for leukaemia and lung cancer were significantly elevated during both transplant function and dialysis after transplant failure, and there was no difference in incidence between periods in multivariate analysis. The standardised incidence ratio for colon cancer was slightly elevated during transplant function but not during dialysis after transplant failure, and there was no difference in incidence between periods in multivariate analysis. Standardised incidence ratios were not elevated in either period for cancers of the breast or prostate, and there was no difference in incidence between periods in multivariate analysis.

DISCUSSION

Among those cancers known to occur at increased rates in kidney transplant recipients, the pattern of incidence during dialysis after transplant failure was highly variable. The incidence of Kaposi's sarcoma and non-Hodgkin's lymphoma (the infection related cancers most strongly related to immunosuppression in both transplant recipients and people infected with HIV) decreased markedly on reinstitution of dialysis. The incidence of lip cancer and melanoma also declined substantially. For each of these four cancer types, standardised incidence ratios were significantly elevated during periods of transplant function, but not during dialysis after transplant failure, suggesting that the effect of immunosuppression on cancer risk was close to completely reversible.

Standardised incidence ratios remained elevated during dialysis after transplant failure for leukaemia and lung cancer, and for cancers known to be related to end stage kidney disease (urinary tract, kidney, thyroid). In fact, the incidence of thyroid cancer was significantly higher during dialysis after transplant failure than during transplant function. There was no significant variation in incidence for other cancers.

Strengths and limitations of the study

This study had several strengths, including the use of national, population based registers of cancer and kidney transplantation, the long period of follow-up, and, unique to the ANZDATA Registry, the availability of comprehensive data on consecutive periods of transplantation and dialysis. The principal limitation was limited statistical power with which to examine incidence beyond the period of first transplantation for the less common cancers. Nevertheless, this is the first epidemiological study to examine site-specific cancer incidence after transplant failure. Much larger studies have the potential to further illuminate the relation between risk of specific cancer types and current immune function.

Comparison with other studies

The reduction in incidence of Kaposi's sarcoma and non-Hodgkin's lymphoma after transplant failure is consistent with a role for current functional immunity in the prevention of these cancers. Both Kaposi's sarcoma and non-Hodgkin's lymphoma are causally associated with infection by γ herpesviruses: Kaposi's sarcoma with human herpesvirus-8, and non-Hodgkin's lymphoma with Epstein-Barr virus in a large proportion of immunodeficient cases.[22] For both cancers, reduction in immunosuppression allows reconstitution of control by herpesvirus-specific CD8 T cells.[23 24] Consistent with the pattern seen in HIV infection,[23] our analyses suggest that restoration of immune function can prevent these cancers from occurring, even in individuals with past intense immunodeficiency. A similar pattern of rapid reduction in risk was not seen for other infection related cancers, although rates were non-significantly lower during dialysis for cancers related to human papillomavirus. Rates of human papillomavirus related cancers decline little, if at all, in the immune reconstitution associated with antiretroviral therapy in people infected with HIV.[4-6]

Lip cancer and melanoma occur at increased rates after solid organ transplantation and in HIV infection.[1] The decline in risk of lip cancer on reinstitution of dialysis was of a similar magnitude to that seen for Kaposi's sarcoma and non-Hodgkin's lymphoma. The precise cause of increased risk of lip cancer in transplant recipients remains unclear, although human papillomavirus may play a role,[25] as may individual immunosuppressive agents.[13] The marked reduction in incidence of cutaneous melanoma observed on reinstitution of dialysis accords with a single previous case report of clinical and dermatoscopic fading of melanocytic naevi after transplant failure and removal of immunosuppression.[26] Melanoma has no known infectious cause, but there is reliable epidemiological and biological evidence of a relation with immune function.[15]

Rates of thyroid cancer are increased in patients with end stage kidney disease, both before and during dialysis, and after kidney transplantation,[18] and are not increased in HIV infection.[1] In our cohort, risk of thyroid cancer was six times higher during dialysis after transplant failure. The higher risk observed during dialysis may reflect the metabolic consequences of chronic renal failure, such as selenium deficiency,[27] which has been linked with thyroid cancer risk in one nested case-control study.[28] Case reports of thyroid

cancer occurring in individuals with secondary hyperparathyroidism induced by hypocalcaemia have also been described.[29]

Rates of leukaemia, and cancers of the stomach, lung, and colon are increased after kidney transplantation[18] and, except for colon cancer, during HIV infection.[1] Risk of these cancers was not associated with currency of immunosuppression in this study; this could suggest that they are not closely related to current immune function or may simply reflect a lack of statistical power. Rates of breast and prostate cancer, which are not increased either after solid organ transplantation or in HIV infection,[1] were not increased at any stage and showed no particular pattern with respect to currency of immunosuppression.

Conclusions and policy implications

The rapid reduction of risk on cessation of immunosuppression for certain viral and immunodeficiency related cancers demonstrates that the effect of immunosuppression is largely reversible for these cancers. An opposite pattern of increased risk during dialysis was observed for thyroid cancer, suggesting that a factor related to end stage kidney disease is important in its pathogenesis. These findings may help inform the management of cancer risk after solid organ transplantation, as well as in HIV infection, where improvements in immune function from new treatments are changing the spectrum of cancer risk. They also offer novel insight into the role of current functional immunity in the prevention of cancer in the general population.

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