

RISK OF CANCER IN RENAL-TRANSPLANT RECIPIENTS

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Summary Among 6297 individuals reported to a kidney-transplant registry, the risk of developing lymphoma was about 35 times higher than normal and was derived almost entirely from a risk of reticulum-cell sarcoma, which was 350 times greater than expected. The excess lymphoma risk appeared within a year of transplantation, and remained at the same high level for the five or more years of follow-up. Skin and lip cancers occurred up to 4 times more often than expected. Other cancers were 2.5 times more common, in men only, due largely to soft-tissue sarcoma and hepatobiliary carcinoma. This excess risk of other cancers appeared later than that for the lymphomas and became more pronounced as the interval since transplantation increased.

Introduction

SINCE 1968 accumulated case-reports have indicated that the risk of cancer, particularly reticulum-cell sarcoma, is increased in recipients of renal transplants.¹⁻³ The size and characteristics of the increased risk have been difficult to determine because few cases came from any one institution, and there was incomplete information on the populations at risk when data from several institutions were pooled.^{4,5}

We have used information collected by a single, large, renal-transplantation registry to compare the risk of various malignancies with that expected on the basis of rates in the general population.

Methods

When a renal transplant was performed at one of 220 participating hospitals in thirty countries, a report was sent to the Human Renal Transplant Registry (American College of Surgeons) containing identifying and demographic information about the recipient and donor.^{6,7}

Follow-up reports on the recipients were made annually by these hospitals. The present study concerned 6297 patients who survived and were followed for at least one month after transplantation during 1951-71. The closing date for follow-up was the end of 1971, but the exact date varied according to institution.

Information on tumours was obtained mainly from routine follow-up inquiries, but additional information was obtained from previously published reports on some of the same cases.^{3,8} 6 individuals with tumours "transplanted" with the donor kidney have been excluded from these analyses, which concerned de-novo tumours only.

The study group was compared with the general population by using the expected numbers of cancers, obtained by the standard method of applying the age, sex, and time specific incidence-rates experienced by the general population to the number of person-years of risk in the study group. The expected numbers of cases were then summed to obtain the total number of expected cases of various forms of cancer. These values were compared with the observed numbers of cases by means of risk ratios (observed/expected). The test of significance is the usual one of comparing an observed random variable with its expectation under the Poisson assumption.⁹ The test of significance for the difference between two or more observed values is the χ^2 test for association.

The incidence-rates used to establish the expected values for all sites except skin and lip were from the Connecticut Cancer Registry.¹⁰⁻¹² Since 90% of the patients were from the United States, Canada, or Western Europe, these rates probably give reasonable approximations of the expected numbers of cancers.

By using preliminary data from the Third National Cancer Survey,¹³ two sets of expected numbers of skin and lip cancers were derived, based on rates from low and high incidence areas in the U.S.A. The true expected value probably lies somewhere between these limits.

In addition to the comparisons with the general population, we conducted a case/control survey of all recipients in whom lymphoma developed. 2 controls were chosen from the registry for each lymphoma case and matched to the case by sex, age, hospital, and year of transplant. This portion of the study used post-transplant therapy and blood-group information that had been collected for some patients during the early years of the registry.

Results

Estimates of Risk

Observed and expected numbers of selected cancers revealed the risk of lymphoma (2.2 per 1000/per year) to be 30 to 40 times that expected both for men and for women (table 1). The excess was due almost entirely to the subcategory of reticulum-cell sarcoma,

which was 350 times more common than expected in both sexes combined. 13 of the 25 recipients with lymphoma had disease localised to the brain (52%), as compared to less than 1% of lymphoma patients in general.¹⁴

There were 21 cases of skin cancer in this population as compared with the 4.99 expected on the basis of rates in a low-incidence area of the U.S.A. This risk was 4.2 times higher than normal, and the increase was statistically significant ($p < 0.01$). On the basis of rates from a high-incidence area, 16.17 cases

TABLE I—OBSERVED AND EXPECTED NUMBERS OF MALIGNANCIES AND RISK RATIOS FOR MEN AND WOMEN WITH RENAL TRANSPLANTS

Malignancy	Males (Total person-years = 7028)			Females (Total person-years = 4196)		
	Observed	Expected	Risk ratio	Observed	Expected	Risk ratio
<i>All lymphomas:</i>	17	0.53	32.1‡	8	0.21	38.1‡
Reticulum-cell sarcoma	14	0.05	280.0‡	7	0.01	700.0‡
Lymphosarcoma	1	0.07	14.3	0	0.03	0.0
Hodgkin's disease	0	0.29	0.0	0	0.09	0.0
Other and unspecified	2	0.12	16.7§	1	0.08	12.5
<i>Other cancers*:</i>	14	5.59	2.5‡	5	5.78	0.9
Lung	2	0.93	2.2	1	0.14	7.1
Liver and biliary	2	0.06	33.3‡	0	0.02	0.0
Breast	0	0.00	...	2	1.55	1.3
All others†	10	4.60	2.2§	2	4.07	0.5

* All sites with the exception of the lymphomas, skin, lip, and in-situ cancer of cervix.

† Observed cases include one each of mouth, stomach (leiomyosarcoma), small-bowel (leiomyosarcoma), colon, ovary, testis, renal pelvis (transitional cell), bladder, melanoma, brain, leukaemia, and metastatic squamous-cell carcinoma (primary unknown).

‡ $P < 0.01$.

§ $P < 0.05$.

were expected and 21 cases were observed. This was an increase of 30% and was not statistically significant. 15 of the 21 cases of skin cancer occurred in patients residing in areas of high risk—Australia and the southwestern portion of the United States.

The risk of other cancers in males was 2.5 times higher than expected (table I). Most of this excess risk was contributed by 2 cases of hepatobiliary cancer (1 hepatocellular carcinoma, 1 bile duct carcinoma) and

2 of leiomyosarcoma (1 arising in stomach and 1 in small bowel). An additional patient with hepatocellular carcinoma and 2 with soft-tissue sarcomas were diagnosed after the cutoff date for follow-up, and were not included in this analysis. In females,

TABLE II—OBSERVED AND EXPECTED NUMBERS OF MALIGNANCIES AND RISK RATIOS ACCORDING TO THE INTERVAL FROM FIRST TRANSPLANT TO TUMOUR DIAGNOSIS

	Interval		
	< 1 yr.	1-5 yr.	> 5 yr.
<i>All lymphomas*:</i>			
Observed	10	13	2
Expected	0.30	0.39	0.05
Risk ratio	33.3	33.3	40.0
<i>Other cancers†:</i>			
Observed	4	8	2
Expected	2.26	2.86	0.47
Risk ratio	1.8	2.8	4.3
<i>Skin and lip cancer‡:</i>			
Observed	2	14	5
Expected (L)	2.09	2.55	0.35
Expected (H)	6.77	8.26	1.14
Risk ratio (L)	1.0	5.5	14.3
Risk ratio (H)	0.3	1.7	4.3

* Both sexes.

† Men only; includes all malignancies other than the lymphomas and skin or lip cancers.

‡ Both sexes; the (H) expected values are based on rates from an area of high incidence, the (L) values from an area of low incidence (see methods).

the risk of other cancers was not increased. No cases of invasive cancer of the cervix were observed, although 2 were expected, but in-situ cervical cancer developed in 5 patients.

The "latent periods" for high-risk categories were estimated by the intervals between first transplantation and cancer diagnosis. The risk of lymphoma increased very early and the size of the excess remained uniform at various times after transplantation (table II). In contrast, the increased risk for other cancers in men and for skin cancers in both sexes appeared later and became more pronounced as the interval since transplantation lengthened.

Characteristics of Risk

The recipient's risk of lymphoma was not influenced by the calendar year of transplantation, number of transplants, country of residence, relationship to the donor, or sex of the donor. There was a significant

TABLE III—OBSERVED AND EXPECTED NUMBERS OF LYMPHOMAS AFTER RENAL TRANSPLANTATION AND RISK RATIOS ACCORDING TO RENAL DISEASE

Recipients' renal disease	All lymphomas		
	Observed	Expected	Risk ratio*
Glomerulonephritis	15	0.45	33.3
Pyelonephritis	1	0.10	10.0
Polycystic kidneys	4	0.04	100.0
Other and unspecified	5	0.15	33.3

* Test for the independence of these values yielded a 3 D.F. χ^2 (with the Yates' correction) of 9.20, $P < 0.05$.

TABLE IV—PERCENTAGE DISTRIBUTION OF ABO BLOOD-GROUPS IN LYMPHOMA CASES, CONTROLS, AND WHITES IN NEW YORK CITY *

Group	% distribution				Total numbers
	A	B	AB	O	
Lymphoma cases	57	21	0	21	14
Controls	32	8	8	52	25
N.Y. City Whites ¹¹	34.6	12.4	7.2	45.8	500

* All patients in the table, except for 2 cases and 7 controls, were Whites from the United States. This association remains essentially the same whether these 9 patients are left in or removed from the comparison.

association with recipient's renal disease, attributed mainly to an increased risk in the few patients with polycystic kidneys (table III). Non-significant increases in lymphoma occurred among recipients first transplanted at a young age (under twenty), among those whose donor was old (over forty-nine), and among those with a large age discrepancy between donor and recipient. Cross-classification of the data implicated the recipient/donor age-difference as the major variable, since adjustment for this variable removes the other two effects. Evaluation of these relations was complicated by the sizeable risk among patients for whom the donor age was unknown.

The case/control survey of records to evaluate the lymphoma risk did not implicate any specific immunosuppressive agent. Information on blood-groups (available on 56% of the lymphoma cases and 50% of the controls) revealed an excess of group A and a deficiency of group O in the lymphoma series, as compared with the distribution in the control group and in a reported sample of the White population in New York City (table IV). The numbers involved are small, however, and the overall difference between cases and controls was not statistically sig-

nificant.

The risk of cancers other than lymphoma among male patients was not significantly related to any variables examined. However, as with lymphoma, there was an increased risk among patients who were young at first transplantation, and whose age was widely different from the donor's age. In contrast with the lymphomas, the risk was somewhat higher in recipients of multiple transplants, and transplants from a donor of the opposite sex. In addition, risk was higher in those who received transplants from a sibling donor (observed=6, expected=1.1), an association which was not explained simply on the basis of the longer survival for this group. Characteristics of the risk of other cancers were not investigated in women recipients, since the risk of such cancers in female renal-transplant recipients was no higher than expected. Similarly, details of the risk of skin and lip cancer were not pursued because the expected rates could not be derived from a population comparable to the transplant population.

Discussion

The risk of lymphoma increased to a maximum within a few months of transplantation, and remained at a uniformly high level over the period of observation. This result differs from previous observations of the pattern of human carcinogenesis in which longer latent periods were associated with a risk which increased with time.¹⁵ Post-transplant lymphomas have also been reported to be more common in the brain.^{16,17}

In contrast with lymphomas, the risk of other post-transplant cancers increased with length of follow-up. This pattern is consistent with that usually seen in carcinogenesis, and suggests that the neoplasms which are excessively common in renal-transplant recipients (sarcomas, liver cancer, skin cancer) may have shorter latent periods or smaller "dose" requirements than tumours which have not yet been found in such patients. As more person-years of experience are collected by the registry, this point should be clarified. Also, regional comparisons can be made for skin cancer, with particular attention to areas of high risk where reliable incidence-rates are available.

Although immunological suppression and antigenic stimuli were probably greater in multiple-transplant recipients, their risk of lymphoma was no greater than

that of single-transplant recipients. However, there was an excessively high risk of cancers other than lymphoma when the donor was a sibling, although immunosuppression was probably less aggressive because of the close "match".^{7 18-20} Since the number of expected cancers was small in any subgroup of transplant recipients, the evaluation of the factors involved in the increased risk of malignancy awaits the accumulation of more data in the registry. It should then be possible to investigate more completely the relations between various neoplasms and multiple transplants and kinship with the donor, and also the relation of lymphoma to polycystic renal disease and to recipient/donor age and perhaps sex interactions.

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