

Original Contributions

CANCER IN PATIENTS RECEIVING LONG-TERM DIALYSIS TREATMENT

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A large excess of non-Hodgkin's lymphoma has been documented in renal transplant patients and may be related to immunosuppressive therapy, persistent antigenic challenge from the graft, or both. To determine whether immunosuppression resulting from chronic renal failure is associated with an elevated risk of certain tumors such as non-Hodgkin's lymphoma, the authors studied cancer incidence in a national cohort of 28,049 patients in the United States with chronic renal failure who received maintenance dialysis for at least six months (totaling 66,706 person-years of observation). Compared with national incidence rates, the relative risk (RR) of cancer was 0.9 (excluding nonmelanoma skin cancer, multiple myeloma, kidney cancer, and uterine cervix cancer). Moderate excesses of leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, thyroid cancer, and biliary tract cancer were found, but were not statistically significant for both sexes combined. A significantly elevated risk of non-Hodgkin's lymphoma among patients with chronic glomerulonephritis (RR = 2.6) accounted for the excess observed in the total series, raising the possibility of factors specific to this disease.

dialysis; glomerulonephritis; immunosuppression; kidney failure, chronic; lymphoma; neoplasms

Epidemiologic studies of cancer in recipients of kidney transplants have shown a

30- to 60-fold increase in the risk of non-Hodgkin's lymphoma, as well as elevated risks for certain other tumors (1-4). However, it is uncertain whether the greatly increased risk of lymphoma first seen in the year after transplant is due to immunosuppressive drug therapy, immunostimulation from the grafted organ, or these factors in combination. An increased risk of lymphoma has been reported in several studies of patients treated with maintenance dialysis for chronic renal failure (5-7) and attributed to the depression of cell-mediated immunity in this group (8). However, other studies of kidney dialysis patients have not found an elevated lymphoma risk (9-13).

To investigate further whether immunosuppression resulting from chronic renal

Received for publication June 20, 1986, and in final form March 31, 1987.

Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

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The authors are indebted to J. Hodges and staff of the Health Care Financing Administration for valuable assistance in obtaining data, and to Dr. T. J. Mason, L. Taylor, L. Shpiegelman, R. Dougherty, Dr. A. Dudgeon, and N. Baugh for professional and technical assistance.

failure unassociated with an organ graft can alter the risk of certain tumors, we analyzed the cancer incidence patterns of a national cohort of 28,049 kidney dialysis patients in the United States who were treated for chronic renal failure without receiving a transplant.

MATERIALS AND METHODS

Data were obtained from the End Stage Renal Disease Program administered by the Health Care Financing Administration of the US Department of Health and Human Services. The program was begun in 1973 to provide reimbursement for medical services to patients with chronic renal failure who needed maintenance dialysis. Nearly all US citizens are entitled to benefits after an initial period of three months on dialysis; 93 per cent of all such patients in the United States receive reimbursement for medical care costs under this program, with the remaining 7 per cent mainly receiving treatment in Veterans Administration hospitals.

Analysis was limited to patients who received benefits during the period from 1973-1979 for whom complete demographic information and medical history (sex, race, birth date, previous malignancy, and underlying renal disease) were submitted at the time of entry into the program; persons with complete records were chosen so that the study group would represent the subset of the End Stage Renal Disease Program patients for whom disease reporting was most likely to be complete. Patients with a history of cancer or those who received a kidney transplant before 1980 were excluded from analysis.

Information on all newly diagnosed cases of cancer was obtained through record review of discharge diagnosis summaries which are routinely supplied to the End Stage Renal Disease Program by hospitals for each inpatient visit regardless of its relation to the treatment of renal failure. To eliminate cancers that may have contributed to the need for dialysis, we ex-

cluded from consideration patients whose cancer was diagnosed during the first three months of coverage in the program. The study group was thus composed of 28,049 patients, i.e., 25,925 patients who became newly eligible for benefits after the inception of the program in 1973 ("incident" cases) and 2,124 patients who had been maintained on renal dialysis for longer than three months prior to that time ("prevalent" cases).

Only first tumors were considered in the analyses presented here. Cancer of the uterine cervix and nonmelanoma skin cancer were excluded, since their detection may be influenced by the frequency of medical care visits, and rates for a large population of comparably supervised persons are not available to estimate expected values. Tumors of the kidney and multiple myeloma were also excluded since these malignancies may be more likely to explain the chronic renal failure than to arise subsequently.

Observed numbers of cancers were compared with the numbers expected based on sex-, race-, and age-specific incidence rates by site from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (14), which provided cancer incidence rates for approximately 10 per cent of the US population from 1973-1977. These rates were applied to the appropriate person-years at risk in the study population. Dialysis patients contributed person-years of risk after three months in the End Stage Renal Disease Program until December 1979 or until the development of a first malignancy or death, if sooner. The ratio of observed to expected cancers, referred to as the relative risk, was calculated for different cancers for the total study population and by underlying renal disease. Analyses were also carried out by interval from entry into the study, by type of dialysis (peritoneal or hemodialysis), and by highest serum creatinine level prior to dialysis. The statistical significance of the difference between the relative risk and 1.0 (no association) and the 95 per cent confidence interval for the relative risks were

calculated assuming an underlying Poisson distribution (15).

RESULTS

Of the 28,049 dialysis patients studied, 56 per cent were male and 71 per cent were white. The mean age at start of maintenance dialysis treatment was 51 years; 49 per cent were aged 45-64 years, and 24 per cent were over age 64 years. The cohort was followed for a total of 66,706 person-years.

Excluding cancer of the kidney, uterine cervix cancer, multiple myeloma, and non-melanoma skin cancer, 405 patients developed a malignancy during the period of follow-up (table 1). Based on sex-, race-, and age-specific incidence rates from the SEER Program (14), 460.0 cases would

have been expected, yielding a relative risk estimate of 0.88. This deficit was statistically significant (95 per cent confidence interval (CI) = 0.7-0.9) and reflects a low relative risk for men. Among male patients, 226 malignancies were reported versus 282.8 expected (relative risk (RR) = 0.8; 95 per cent CI = 0.7-0.9). Among female patients, 179 tumors were reported versus 177.2 expected (RR = 1.0; 95 per cent CI = 0.9-1.2). Relative risks were similar for whites and nonwhites and for incident and prevalent patients.

As shown in table 1, for both sexes combined, nonsignificant excesses by site were observed for thyroid cancer (RR = 2.2), leukemia (RR = 1.5), Hodgkin's disease (RR = 2.0), non-Hodgkin's lymphoma (RR = 1.2), biliary tract cancer (RR = 1.8), and

TABLE 1
Relative risk of malignancies among renal dialysis patients,* United States, 1973-1979

	Males		Females		Total	
	RR†	No. observed	RR	No. observed	RR	No. observed
All cancers‡	0.8§	226	1.0	179	0.9§	405
Buccal cavity, pharynx	0.6	8	0.7	3	0.6	11
Esophagus	0.6	4	1.1	2	0.7	6
Stomach	0.7	8	0.8	3	0.7	11
Large intestine	0.8	21	1.1	21	0.9	42
Rectum	0.4§	5	0.4	3	0.4§	8
Liver	0.4	1	2.4	2	0.9	3
Gallbladder, bile ducts	2.7	2	1.1	1	1.8	3
Pancreas	0.6	6	0.9	5	0.7	11
Bronchus, lung	0.8	57	1.1	18	0.8	75
Soft tissue	2.2	3	—	0	1.4	3
Melanoma	0.3	1	2.1	5	1.0	6
Breast (females)			0.7	41	0.7	41
Uterus			0.6	11	0.6	11
Ovary			0.5	5	0.5	5
Prostate	0.6§	34			0.6§	34
Urinary bladder	0.7	12	1.8	7	0.9	19
Brain	—	0§	1.4	3	0.5	3
Thyroid	1.2	2	2.9§	6	2.2	8
Hodgkin's disease	1.2	2	2.8	5	2.0	7
Non-Hodgkin's lymphoma	1.3	9	1.1	5	1.2	14
Leukemia	1.4	11	1.6	6	1.5	17
Other	1.1	17	1.9	9	1.3	26
Ill-defined, unspecified	2.1§	23	2.7§	18	2.4§	41

* Includes all 28,049 patients at risk.

† RR, relative risk.

‡ Excludes nonmelanoma skin cancer, multiple myeloma, cancer of the kidney, and uterine cervix cancer.

§ $p < 0.05$.

|| Not calculable, with no cases observed.

- patients with chronic renal failure on long-term dialysis. *Clin Nephrol* 1976;5:101-4.
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mismatch) were associated with lymphoma risk, although this pattern was not observed in the study by Kinlen et al. (3). While patients with chronic renal failure may also be antigenically challenged (e.g., by hepatitis B infection, bacteremia, and infection of an external shunt), such immunostimulation differs from that associated with organ transplantation.

Dialysis patients with glomerulonephritis and renal transplant recipients share certain characteristics that may explain their susceptibility to certain tumors. Immunosuppressive drug therapy used to prevent graft rejection is given for some forms of glomerulonephritis, and patients with glomerulonephritis may also be immunostimulated through autoimmune mechanisms. Thus, in both conditions, the risk of lymphoma and perhaps certain other cancers may be related to the intensity of both immunosuppression and antigenic stimulation.

Our finding that there was no large increase in the risk of non-Hodgkin's lymphoma is in agreement with some (9-13), but not all (5-7), previous cohort studies of dialysis patients. The largest of these studies (5) followed 1,651 patients from the United Kingdom until 1976 and found a twentyfold increased risk for non-Hodgkin's lymphoma based on four cases. The much smaller excess risk of this tumor that we observed may reflect changes over time or differences between these two countries in medical management (19, 20). It will be of interest to determine whether more recent data from the United Kingdom show findings similar to ours.

Hemodialysis patients are at increased risk of exposure to hepatitis B, a suspected risk factor for hepatocellular carcinoma (21), and exposure to diethylhexylphthalate which is leached from plastic tubing in hemodialysis equipment and is reported to cause liver cancer in animal studies (22). While no increase in the risk of liver cancer was observed among the dialysis patients we studied, follow-up may not yet be long enough to detect an elevated risk. Deficits

seen for prostate and rectum cancer in this population may have resulted from possible increased detection prior to enrollment in the End Stage Renal Disease Program, but a relation between dietary restrictions for chronic renal disease and protection in these tumors may be involved (23, 24).

In summary, we found no overall increase in cancer risk for this large population of dialysis patients, and no large relative risk for lymphoma as seen in transplant recipients. Thus, it seems unlikely that the immunosuppressive consequences of chronic renal failure contribute to the high risk of certain malignancies among renal transplant recipients. In the subgroup of dialysis patients with glomerulonephritis, however, there was an excess of certain tumors that are also increased in transplant recipients, but at a much lower level of risk. Further studies aimed at exploring factors such as immunosuppressive drug therapy would be of value in delineating causal mechanisms.

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TABLE 3
Relative risk of selected malignancies among dialysis patients with and without glomerulonephritis,
 United States, 1973-1979*

	Dialysis patients with glomerulonephritis		All other dialysis patients	
	RR†	No. observed	RR	No. observed
All cancers‡	0.9	92	0.9	288§
Non-Hodgkin's lymphoma	2.6	7§	0.8	6
Biliary tract cancer	2.6	2	1.2	1
Melanoma	2.1	3	0.8	3
Other	0.8	80	0.9	278

* Incident patients only.

† RR, relative risk.

‡ Excludes nonmelanoma skin cancer, multiple myeloma, cancer of the kidney, and uterine cervix cancer.

§ $p < 0.05$.

relative risk of cancer was not significantly different from unity.

The vast majority of patients in this series were maintained on hemodialysis (97 per cent), with the remainder treated with peritoneal dialysis. The relative risk of malignancy was similar for these two groups of patients. However, with peritoneal dialysis, there was a nonsignificant excess of non-Hodgkin's lymphoma (RR = 7.9 based on two cases). This increased risk was not seen in hemodialysis patients and was not explained by an association with glomerulonephritis.

Cancer risk did not vary by highest serum creatinine level prior to dialysis among patients whose medical history included this information (32 per cent of patients).

DISCUSSION

The present study revealed no overall increase in cancer risk in a large population of dialysis patients and no change in risk with length of dialysis treatment. In addition, no large increase in the relative risk of lymphoma was observed. In contrast, a more than twofold increased risk of cancer has been reported among transplant recipients, largely due to a high risk of lymphoma (2, 4). The absence of an increase in cancer risk among patients or a greatly elevated lymphoma risk suggests that the immunosuppressive consequences of

chronic renal failure contribute little to the elevated cancer risks reported among transplant recipients.

In the subgroup of dialysis patients with glomerulonephritis, however, there was an excess of certain tumors that are also increased in transplant recipients, although at a lower level of risk. Thus, for non-Hodgkin's lymphoma the relative risk with glomerulonephritis was 2.6, compared with a 30-fold risk reported in transplant recipients (2). The relative risk of biliary tract cancer associated with glomerulonephritis was also 2.6, compared with a substantially increased risk in transplant recipients (4). However, the risk of melanoma with glomerulonephritis was similar to that reported in transplant recipients (3, 4).

Differences in immune status between dialysis and transplant patients may explain these findings. In contrast to the drug-induced suppression of cellular immune function in transplant recipients, chronic renal failure depresses but does not arrest normal immune response (8, 16, 17). Posttransplant stimulation of the immune system due to a foreign graft may also contribute to the elevated risk of malignancy, notably non-Hodgkin's lymphoma. In two studies (4, 18), several parameters reflecting immunostimulation (e.g., repeated transplantation, cadaver-vs.-sibling organ graft, and human leukocyte antigen

soft tissue cancers (RR = 1.4). Although risk of melanoma was not increased overall, there was a nonsignificant twofold excess in women. The elevated risk of thyroid cancer was due to a significant threefold excess in women. The elevated risk of Hodgkin's disease reflects a large excess among nonwhite women (RR = 26.7) based on four cases. The small increase in the risk of biliary tract and soft tissue cancers represents an excess among men only based on small numbers. An excess of ill-defined and unspecified tumors was seen in both sexes, reflecting the slightly lower proportion of specific diagnoses reported to the End Stage Renal Disease Program compared with the SEER tumor registries used for expected values. The relative risks of prostate cancer (RR = 0.6) and brain cancer (RR = 0; 3.98 cases expected) in men were significantly low, accounting in part for the lower overall risk of malignancy in men. A significantly lower risk of rectal cancer (RR = 0.4) was observed in both sexes.

The risk of total cancer by year of follow-up remained constant during the first five years, but certain tumors showed some variations with time (table 2). The risk of lymphomas remained modestly elevated during the first two years of follow-up,

while the increase of leukemia was limited to the first year. The elevated risk of thyroid cancer was not clearly related to time, but the relative risk of lung cancer showed a modest increase, to reach 1.4 after five years of follow-up.

Risk patterns for malignancy were also examined by type of primary renal disease. Most common was glomerulonephritis (25 per cent of patients), followed by primary hypertensive disease (19 per cent), diabetic nephropathy (14 percent), interstitial nephritis (10 per cent), and polycystic kidney disease (8 per cent). The risks of total cancer, leukemia, and thyroid cancer among incident patients with these diseases were not significantly different from unity. However, as shown in table 3, patients with glomerulonephritis experienced elevated risks for non-Hodgkin's lymphoma (RR = 2.6), malignant melanoma (RR = 2.1), and biliary tract cancer (RR = 2.6), although the numbers involved were small. In particular, the excess of non-Hodgkin's lymphoma among glomerulonephritis patients accounts entirely for the slight elevation in risk observed for the total series. Among patients with less common renal diseases (collagen vascular disease, acquired obstructive uropathy, hereditary interstitial disease, and analgesic nephropathy), the

TABLE 2
Relative risk of selected malignancies among dialysis patients by year from entry into study,*
United States, 1973-1979

	Year from entry into study							
	<1		1-2		3-4		≥5	
	RR†	No. observed	RR	No. observed	RR	No. observed	RR	No. observed
All cancers	0.9	146	0.9	166	0.9	61	0.6	7
Non-Hodgkin's lymphoma	1.5	6	1.3	6	0.6	1	—‡	0
Hodgkin's disease	3.6	3	2.2	2	—	0	—	0
Leukemia	2.9§	12	0.7	3	—	0	—	0
Thyroid cancer	1.7	2	2.9	4	1.8	1	—	0
Lung cancer	0.7	22	0.9	32	1.1	15	1.4	3

* Incident patients only. Excludes nonmelanoma skin cancer, multiple myeloma, cancer of the kidney, and uterine cervix cancer.

† RR, relative risk.

‡ Not calculable, with no cases observed.

§ $p < 0.05$.