# Cancer in patients receiving dialysis

L J KINLEN, J B EASTWOOD, D N S KERR, J F MOORHEAD, D O OLIVER, B H B ROBINSON, H E DE WARDENER, A J WING


## Summary and conclusions

**The incidence of cancer and related mortality was studied in 1651 patients from six dialysis centres in England over 10 years. The only type of cancer for which there was a significant excess was non-Hodgkin's lymphoma (four cases observed against an expected incidence of 0·15 ($p < 0·001$); three deaths against an expected 0·1 ($p < 0·001$)). This excess could not be attributed to either subsequent transplantation or treatment with immunosuppressive drugs.**

**Since immunodepression is a feature of chronic renal failure, these observations together with those on patients treated with immunosuppressive drugs suggest that immunosuppression favours the development of non-Hodgkin's lymphoma. Studies in which it is concluded that patients receiving dialysis show an excess of other types of cancer have certain shortcomings; the unusual opportunities for detecting cancer in such patients may account for some of the reported excess.**


## Introduction

Renal transplant recipients show an increased incidence of certain cancers, particularly non-Hodgkin's lymphoma.[1 2] An increased incidence of tumours in patients with chronic renal failure was reported by Matas *et al* and attributed to the immunosuppressive effects of uraemia.[3] Other studies, though arriving at a similar conclusion, did not estimate expected numbers of cancers for comparison with those observed.[4-8] Moreover, none of those studies reported an increase in *mortality* from cancer. We conducted this study to determine the incidence of cancer and its associated mortality in the patients of several large dialysis centres in England.

## Patients and methods

The study population consisted of patients receiving dialysis in six large dialysis centres—in Oxford, Newcastle upon Tyne, Birmingham and certain associated hospitals, and London. Details of these patients were taken from the files of the European Dialysis and Transplant Association and included age; underlying renal disorder; and dates of first peritoneal dialysis and haemodialysis, transplantation, failure of graft function, and death. The association's records were checked for completeness against the respective centre's own records, and the few omitted cases detected were incorporated into the study. The choice of centres was made on independent advice based on their size and length of operation; it was also made without knowledge of cases of cancer recorded in those centres. Patients who were dialysed on account of renal failure due to malignant disease were excluded from the analysis.

Details of cases of cancer were obtained from the centres, and in fatal cases a copy of the death certificate was obtained from the Office of Population Censuses and Surveys to determine if the cause of death was given as malignancy. Person-years at risk were calculated up to 31 December 1976 (or up to the date of death or transplantation if before that date) by five-year age group, sex, and calendar year, and expected numbers of deaths from cancer and cases of cancer were obtained by multiplying these by the corresponding mortality rates for England and Wales and rates of incidence obtained from the Birmingham Cancer Registry.[9] The data were analysed in two ways, the point of entry being the date of first dialysis (often peritoneal) for the first analysis, and the date of first haemodialysis for the second. In these analyses, the effects of foreign antigens and immunosuppressive drugs were eliminated by "censoring" patients when they underwent transplantation, their subsequent experience contributing to neither observed nor expected incidence and mortality.

## Results

All the patients (1651) underwent haemodialysis or peritoneal dialysis at the study centres in the period covered by the European Dialysis and Transplant Association's records, and of these 1651, 845 later underwent transplantation. Table I shows the numbers of patients in each age group, sex, whether transplantation was performed, and the person-years at risk. The principal underlying disorders were chronic glomerulonephritis, chronic pyelonephritis, and polycystic disease, with smaller numbers of patients suffering from other acquired and congenital renal disorders (table II).

TABLE I—*Numbers of patients receiving dialysis grouped according to age and sex*

| Age group (yr) | Patients who never received a transplant | | All patients | | | |
|---|---|---|---|---|---|---|
| | M | F | M | F | Total | Person-years |
| 0-9 | 2 | 6 | 6 | 13 | 19 | 18·8 |
| 10-19 | 34 | 29 | 90 | 67 | 157 | 207·1 |
| 20-29 | 94 | 65 | 206 | 155 | 361 | 760·1 |
| 30-39 | 126 | 71 | 272 | 163 | 435 | 1254·4 |
| 40-49 | 142 | 95 | 275 | 179 | 454 | 1210·3 |
| 50-59 | 89 | 40 | 143 | 66 | 209 | 658·5 |
| ⩾60 | 8 | 5 | 10 | 6 | 16 | 85·0 |
| All ages | 495 | 311 | 1002 | 649 | 1651 | 1494·2 |

Table III shows the observed and expected numbers of deaths from cancer and incidence of cancer in patients receiving dialysis. The results for non-Hodgkin's lymphoma are shown separately because its greatly increased incidence in transplant recipients is of particular interest in view of the incidence of these tumours in patients receiving dialysis. There was a significant excess mortality from non-Hodgkin's lymphoma (three deaths observed against 0·10 expected; $p < 0·001$) but no significant excess of deaths from other tumours (five observed against 4·53 expected). The incidence of non-Hodgkin's lymphoma was also significantly raised (four cases against 0·15 expected;

**Radcliffe Infirmary, Oxford OX2 6HE**
L J KINLEN, DPHIL, MRCP, Cancer Research Campaign Gibb fellow

**Department of Medicine, Charing Cross Hospital, London W6 8RF**
J B EASTWOOD, MD, MRCP, lecturer in medicine
H E DE WARDENER, MD, FRCP, professor

**Department of Medicine, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP**
D N S KERR, FRCP, professor

**Department of Nephrology and Transplantation, Royal Free Hospital, London NW3 2QG**
J F MOORHEAD, FRCP, consultant physician and director

**Renal Unit, Churchill Hospital, Oxford**
D O OLIVER, FRCP, consultant physician

**East Birmingham Hospital, Birmingham B9 5ST**
B H B ROBINSON, FRCP, consultant physician

**St Thomas's Hospital, London SE1 7EH**
A J WING, DM, FRCP, consultant physician

TABLE II—*Numbers of patients receiving dialysis grouped according to underlying disease and sex*

| Underlying renal disorder | Patients who never received a transplant | | All patients | | |
|---|---|---|---|---|---|
| | M | F | M | F | Both sexes |
| Chronic glomerulonephritis | 229 | 94 | 501 | 225 | 726 |
| Chronic pyelonephritis .. | 55 | 77 | 95 | 169 | 264 |
| Polycystic disease .. .. | 52 | 28 | 93 | 54 | 147 |
| Renal vascular disease .. | 53 | 26 | 93 | 41 | 134 |
| Other specified disorders .. | 84 | 74 | 178 | 133 | 311 |
| Uncertain diagnosis .. .. | 22 | 12 | 42 | 27 | 69 |
| Total .. .. .. | 495 | 311 | 1002 | 649 | 1651 |

TABLE III—*Deaths from cancer and incidence of cancer in patients receiving dialysis. Corresponding results after first haemodialysis shown in parentheses*

| Cancer type | Observed | Expected |
|---|---|---|
| *Deaths* | | |
| Non-Hodgkin's lymphoma .. | 3 (2) | 0·10 (0·09) |
| Other .. .. .. .. | 5* (5) | 4·53 (4·36) |
| Total .. .. .. | 8 (7) | 4·63 (4·45) |
| *Incidence* | | |
| Non-Hodgkin's lymphoma .. | 4 (4) | 0·15 (0·14) |
| Other .. .. .. .. | 11† (11) | 8·29 (7·97) |
| Total .. .. .. | 15 (15) | 8·44 (8·11) |

*Consisting of two deaths from hypernephromas, one from renal pelvis cancer, one from stomach cancer, and one from cancer of uncertain primary origin.
†Consisting of two hypernephromas; two thyroid cancers; and one case of each of the following cancers: renal pelvis, breast, stomach, bladder, astrocytoma, in situ of cervix, and of uncertain primary origin.

$p < 0.001$). The slight excess of other cancers (11 cases observed, 8·29 expected) was not significant. Moreover, three of these tumours (two thyroid and one cervical in situ) were asymptomatic and therefore more likely to be detected in the patients receiving dialysis, who were closely supervised, than in the general population from which the expected figures were derived. Another case that should perhaps be considered separately was the renal pelvis cancer that occurred in a patient with analgesic nephropathy, since a relation between these disorders is established in the absence of dialysis.[10] Not included among the 11 observed cancers were six noninvasive renal tumours detected in a careful postmortem study at one of the centres,[11] since these were not considered malignant.

There is sometimes an appreciable interval between initial dialysis (often peritoneal) and regular haemodialysis; the analyses were therefore repeated from the date of first haemodialysis. The observed numbers of deaths from cancer were unaffected, and the expected numbers altered only slightly (table III).

Table IV shows the details of the four cases of non-Hodgkin's lymphoma. In case 4, which has been reported separately,[12] the lymphoma (confined to the brain) was diagnosed 22 months after first dialysis for chronic renal failure caused by polycystic disease. The other three lymphomas occurred in patients whose renal failure was caused by chronic pyelonephritis (two cases) or chronic glomerulonephritis (one case). No patient had taken immunosuppressive drugs, such as cyclophosphamide or azathioprine.

## Discussion

The only type of cancer that showed a significant excess both in incidence and associated mortality among patients receiving dialysis was non-Hodgkin's lymphoma. The small and non-significant excess of other cancers can be explained by the better detection of tumours in such a closely supervised group of patients compared with the general population and by the inclusion of a case related to the underlying renal disease.

Renal impairment, particularly the nephrotic syndrome, may be the first manifestation of an extrarenal neoplasm such as bronchial or colonic cancer or Hodgkin's disease, but this seems unlikely to be the reason for an excess of non-Hodgkin's lymphoma in patients receiving dialysis. Nearly all the lymphomas reported as presenting in this way are cases of Hodgkin's disease after development of the nephrotic syndrome,[13-19] whereas none of our cases were of either the nephrotic syndrome or Hodgkin's disease. Moreover, the diverse renal pathology (chronic glomerulonephritis, chronic pyelonephritis, and polycystic disease) also reduces the likelihood of the renal disorder being caused by the lymphoma.

Most reports of cancer in patients with chronic renal failure have not included expected numbers, so it is difficult to evaluate whether their findings indicate that such patients show an increased incidence of cancer.[4 5 7 8] Matas *et al*[3] observed a significant excess of cancer (11 cases observed against under two expected), but the larger study by Slifkin *et al*[20] did not (22 cases observed, 21·84 expected). The second study,[20] however, recorded an excess of reticulum-cell sarcoma (two cases observed against 0·3 expected). The large excess reported by Matas *et al* may be partly artefactual, as none of the cancers had caused death, two were diagnosed before the patients were referred for dialysis, and two (a clear-cell adenoma of the kidney and an insulinoma) may not have been malignant. Moreover, the unusual opportunities for detecting cancer in such closely supervised patients might explain the diagnosis of the cervical cancer in situ and perhaps also the cases of thyroid cancer and chronic lymphatic leukaemia, since these are often asymptomatic.

Both renal transplantation and treatment with immunosuppressive drugs in the absence of foreign antigens are associated with an increased incidence of non-Hodgkin's lymphoma.[2] Our finding of an excess of non-Hodgkin's lymphoma in a group of patients receiving dialysis cannot, however, be attributed to either of these influences. Chronic renal failure is associated with some depression of the immune system,[21] which suggests that immunosuppression of any type favours the development of non-Hodgkin's lymphoma. The possibility of a viral origin of these tumours in transplant recipients has been discussed.[2] Two of the four lymphomas in our patients were diagnosed within a year of first dialysis, and this unusually short induction period would be consistent with malignant transformation by a virus that was already present. The relative excess of non-Hodgkin's lymphoma in our series (26:1) is intermediate between that observed in transplant recipients (58:1) and that in patients treated with immunosuppressive drugs without receiving a transplant (11:1).[2] The number of cases, however, is

TABLE IV—*Details of cases of non-Hodgkin's lymphoma (NHL) in patients receiving dialysis. None of the four patients had undergone transplantation*

| Case No | Sex | Age at 1st dialysis (yr) | Date of 1st dialysis | Date of 1st haemodialysis | Underlying disorder | Date of diagnosis of NHL | Outcome |
|---|---|---|---|---|---|---|---|
| 1 | M | 31 | Aug 1975 | Nov 1975 | CGN | Nov 1975 | Died, Jan 1976 |
| 2 | M | 31 | May 1966 | May 1966 | CPN | July 1971 | Died, Sept 1971 |
| 3 | M | 57 | Oct 1974 | May 1975 | CPN | June 1975 | Died, Nov 1976 |
| 4 | M | 47 | June 1971 | June 1971 | Polycystic disease | April 1973 | Alive, Dec 1976 |

CGN = Chronic glomerulonephritis.
CPN = Chronic pyelonephritis.

small, and a larger series of patients is needed to estimate the size and persistence of the excess more precisely. It will be interesting to determine from such a series if there is also an excess of soft tissue sarcomas and squamous cell cancer of the skin, which are also increased in incidence in renal transplant patients.

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Requests for reprints should be addressed to L J Kinlen.

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# Alcohol consumption and premature death in middle-aged men

BO PETERSON, HANS KRISTENSON, NILS H STERNBY, ERIK TRELL, GÖRAN FEX, BERTIL HOOD


## Summary and conclusions

**All the men living in Malmö born in 1926-9 were invited for a screening examination which included an assessment of alcohol consumption and measurement of gamma-glutamyltransferase (GGT) activity. They were followed for up to four years (median 2) and their mortality assessed. Sixty-two deaths occurred, 41 (0·9%) among the 4571 men who attended the screening investigation and 21 (1·3%) among the 1609 who did not respond to the invitation. Evidence of alcohol abuse or an alcohol-related cause of death was present in 25 (61%) of the deaths among the attenders and 13 (62%) of those among the non-responders. GGT values at the screening investigation were significantly increased in 19 (46%) of those who died, but established risk factors, such as cholesterol and triglyceride concentrations and blood pressure, had little predictive value.**

**Measurement of GGT provided an objective index of alcohol consumption, though the full clinical importance of a raised value needs further assessment. The finding that heavy alcohol consumption was the single most important factor associated with premature death in these middle-aged men has important implications for prevention.**


**Section of Preventive Medicine, Departments of Internal Medicine, Alcohol Diseases, Pathology, and Clinical Chemistry, University of Lund, Malmö General Hospital, S-214 01 Malmö, Sweden**

BO PETERSON, MD, associate researcher in preventive medicine
HANS KRISTENSON, MD, associate researcher in alcohol diseases
NILS H STERNBY, MD, professor of pathology
ERIK TRELL, MD, associate professor of preventive medicine
GÖRAN FEX, MD, associate professor of clinical chemistry
BERTIL HOOD, MD, professor of medicine

## Introduction

Though alcohol is recognised to be a major contributory factor in disease and premature death among middle-aged men, the medical profession still tends to underestimate the importance of alcohol in the range of disease.[1] There have been demands for a "public health strategy" to identify and prevent alcohol abuse through screening[2 3] and for powerful political and economic measures to curb consumption. An important pre-requisite for any of these measures is increased knowledge of the medical complications of alcohol consumption.

We established a screening clinic to try to identify and prevent alcohol abuse, and we report here a study on the short-term mortality of middle-aged men who were invited for screening.