Cancers of the Kidney and Urinary Tract in Patients on Dialysis for End-Stage Renal Disease: Analysis of Data from the United States, Europe, and Australia and New Zealand

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Abstract. Patients on maintenance dialysis have increased risk for cancer, especially in the kidney and urinary tract. In a retrospective cohort of 831,804 patients starting dialysis during 1980 to 1994 in the United States, Europe, or Australia and New Zealand, standardized incidence ratios (SIR) with 95% confidence intervals (CI) were calculated for kidney and bladder cancers. Risks for cancers of the kidney (SIR 3.6; CI 3.5 to 3.8) and bladder (SIR 1.5; CI 1.4 to 1.6) were increased, relatively more in younger than older patients and more in female patients (kidney: SIR 4.6, CI 4.3 to 4.9; bladder: SIR 2.7, CI 2.4 to 2.9) than male patients (kidney: SIR 3.2, CI 3.0 to 3.4; bladder: SIR 1.3, CI 1.2 to 1.3). SIR for kidney cancer were raised in all categories of primary renal disease, and for bladder cancer in all but diabetes and familial, hereditary diseases. Notably high SIR occurred in toxic nephropathies (chiefly analgesic nephropathy) and miscellaneous conditions (a category that includes Balkan nephropathy), the excess of kidney cancer in these conditions being urothelial in origin. SIR for kidney cancer rose significantly, and those for bladder cancer fell (not reaching significance) with time on dialysis. There was no association with type of dialysis. The pattern of increased risk for renal parenchymal cancer in dialysis patients is consistent with causation through acquired renal cystic disease and of urothelial cancers of the kidney and bladder with the carcinogenic effects of certain primary renal diseases.

In this article, we have examined population-based data from three large dialysis registries to clarify current understanding of the nature of the excess of cancers of the kidney and urinary tract in patients with ESRD treated by maintenance dialysis and identify the risk factors that may be responsible.

Materials and Methods

Inclusion and Exclusion Criteria

We assembled a retrospective cohort of 831,804 patients who received dialysis for ESRD during the period from 1980 to 1994 (1) in the United States (USRDS) (11), Europe (EDTA) (12), or Australia and New Zealand (ANZDATA) (13). Excluded were patients: with missing date of birth or follow-up data; who had AIDS, were receiving dialysis after transplantation, or were treated in regions for which suitable background cancer rates were unavailable; and those in whom the diagnosis of cancer preceded dialysis. The primary causes of ESRD were grouped into ten categories (14).

Statistical Analyses

We calculated the number of person-years at risk from the date of first dialysis until the date of last contact, transplantation or death. The
expected numbers of cancers of the kidney (ICD-9 189: this rubric includes urothelial cancers arising from the renal pelvis, ureter, or urethra as well as all cancers of the renal parenchyma, chiefly adenocarcinomas and bladder (ICD-9 188) were calculated by multiplying the number of person-years accumulated in each stratum of age, gender, race (for USRDS patients only), country, and calendar-time by the corresponding background-specific rate (1,15,16). The standardized incidence ratio (SIR), the ratio of observed to expected cancers, was used to estimate the relative risk, and the Wilcoxon-Mann-Whitney test was used to assess trend of the risk over time on dialysis. COX proportional hazards regression models were used to evaluate the effect of explanatory variables on the time to develop kidney or bladder cancer. Subjects were right censored if they were alive at the end of the study period, known to be alive at some time but subsequently lost to follow-up, or transplanted. Kaplan Meier plots showing time to diagnosis of cancer were included only for their illustrative value.

**Results**

In this population of 831,804 patients with ESRD treated by maintenance dialysis followed for 2,045,035 person-years (Table 1), there were 2053 incident cancers of the kidney when 570 were expected (SIR 3.6; CI 3.5 to 3.8; \( P < 0.0001 \)) and 1646 incident cancers of the bladder compared with 1100 expected (SIR 1.5; CI 1.4 to 1.6; \( P < 0.0001 \); Table 2; Figure 1). The excess was observed at all ages and in both genders, but it was relatively more pronounced in the young (Figures 2 and 3) and was greater in female than in male patients (Table 2; Figures 2 and 3).

**Risk of Kidney Cancer**

The increased risk of kidney cancer occurred in every category of primary renal disease, being greatest in congenital diseases (Obs 10; SIR 12.5; CI 6.0 to 23.0), toxic nephropathies (Obs 166; SIR 11.8; CI 10.0 to 13.7), and miscellaneous conditions (Obs 56; SIR 6.6; CI 5.0 to 8.5) (Table 2). The excess incidence in the latter two categories was largely attributable to analgesic nephropathy (Obs 146; SIR 16.7; CI 14.1 to 19.6), seen principally in Australia and Europe, and Balkan nephropathy (Obs 11; SIR 26.2; CI 13.1 to 46.9), seen almost exclusively in Europe, respectively. Patients with ESRD due to diabetes exhibited the lowest excess risk (Obs 278; SIR 2.4; CI 2.1 to 2.7), significantly less than that of any other category of primary renal disease except familial, hereditary diseases (comprising 88 to 92% polycystic kidney disease) (14).

**Risk of Bladder Cancer**

Bladder cancer showed a similar pattern of excess risk, but with generally fewer observed cases and lower SIR than for kidney cancer (Table 2). The highest SIR were seen in the same three categories of primary renal disease: toxic nephropathies (Obs 167; SIR 7.3; CI 6.2 to 8.4); congenital diseases (Obs 6; SIR 4.4; CI 1.6 to 9.6); and miscellaneous conditions (Obs 54; SIR 2.9; CI 2.2 to 3.8). Infective and obstructive nephropathies also showed an excess risk significantly higher than that of all patients combined (Obs 313; SIR 2.5; CI 2.3 to 2.8). Similar to kidney cancer, the excess risk for bladder cancer in toxic nephropathies and miscellaneous conditions was largely, but not entirely, attributable to analgesic nephropathy (Obs 145; SIR 13.3; CI 11.3 to 15.7) and Balkan nephropathy (Obs 12; SIR 18.2; CI 9.4 to 31.8), respectively. Neither diabetes nor familial hereditary diseases showed an excess risk of bladder cancer.

**Association of Type of “Kidney” Cancer with Primary Renal Disease**

The ANZDATA Registry had recorded the histologic type of "kidney" cancer (Table 3), and the EDTA Registry the sub-site location of the cancer (Table 4); the corresponding information was not available for USRDS patients. “Kidney” cancers of urothelial origin (transitional cell carcinomas in Table 3, cancers of the renal pelvis, ureter, or urethra in Table 4) were the majority in patients with toxic nephropathies and also comprised a quarter or more of “kidney” cancers in patients with infective and obstructive nephropathies and, in Europe, miscellaneous conditions. In all other categories of primary renal disease, the excess risk was largely attributable to analgesic nephropathy (Obs 146; SIR 16.7; CI 14.1 to 19.6), seen principally in Australia and Europe, and Balkan nephropathy (Obs 11; SIR 26.2; CI 13.1 to 46.9), seen almost exclusively in Europe, respectively. Patients with ESRD due to diabetes exhibited the lowest excess risk (Obs 278; SIR 2.4; CI 2.1 to 2.7), significantly less than that of any other category of primary renal disease except familial, hereditary diseases (comprising 88 to 92% polycystic kidney disease) (14).

**Table 1. Characteristics of study population**

<table>
<thead>
<tr>
<th></th>
<th>ANZDATA (Australia, New Zealand)</th>
<th>EDTA (Europe)</th>
<th>USRDS (United States)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>13,497</td>
<td>296,903</td>
<td>521,404</td>
</tr>
<tr>
<td>Mean age at 1st dialysis (yr)</td>
<td>48.7</td>
<td>51.8</td>
<td>57.8</td>
</tr>
<tr>
<td>Mean duration of follow-up (yr)</td>
<td>2.55</td>
<td>2.89</td>
<td>2.21</td>
</tr>
<tr>
<td>Male/female patients</td>
<td>55.7% / 44.3%</td>
<td>58.4% / 41.6%</td>
<td>53.4% / 46.6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of dialysis</th>
<th>n</th>
<th>%</th>
<th>yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>hemodialysis</td>
<td>5869</td>
<td>43.4</td>
<td>2.4</td>
</tr>
<tr>
<td>mixed hemo/peritoneal</td>
<td>4475</td>
<td>33.2</td>
<td>3.2</td>
</tr>
<tr>
<td>peritoneal dialysis</td>
<td>3153</td>
<td>23.4</td>
<td>1.9</td>
</tr>
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</table>

* Mean time on dialysis.
Table 2. Numbers of observed (Obs) and expected (Exp) kidney and bladder cancers with corresponding standardized incidence ratios (SIR) and 95% confidence intervals (CI)

<table>
<thead>
<tr>
<th></th>
<th>Kidney Cancer (ICD-9 189)</th>
<th>Bladder Cancer (ICD-9 188)</th>
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<tr>
<td></td>
<td>Obs</td>
<td>Exp</td>
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<tr>
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<td>569.9</td>
</tr>
<tr>
<td>Registry</td>
<td></td>
<td></td>
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<td>ANZDATA (Australia, New Zealand)</td>
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<tr>
<td>EDTA (Europe)</td>
<td>680</td>
<td>206.5</td>
</tr>
<tr>
<td>USRDS (United States)</td>
<td>1303</td>
<td>356.2</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>male patients</td>
<td>1254</td>
<td>395.6</td>
</tr>
<tr>
<td>female patients</td>
<td>799</td>
<td>174.3</td>
</tr>
<tr>
<td>Time after 1st dialysis</td>
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<td></td>
</tr>
<tr>
<td>during year 1</td>
<td>632</td>
<td>197.5</td>
</tr>
<tr>
<td>during year 2</td>
<td>386</td>
<td>122.8</td>
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<tr>
<td>during years 3 to 5</td>
<td>630</td>
<td>171.6</td>
</tr>
<tr>
<td>during years 6 to 10</td>
<td>351</td>
<td>70.5</td>
</tr>
<tr>
<td>after year 10</td>
<td>54</td>
<td>7.9</td>
</tr>
<tr>
<td>Type of dialysis</td>
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<tr>
<td>hemodialysis</td>
<td>1518</td>
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<td>mixed hemo/peritoneal</td>
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<td>peritoneal dialysis</td>
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<td>Primary renal disease</td>
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<tr>
<td>arteriopathic renal diseases</td>
<td>526</td>
<td>153.2</td>
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<td>272</td>
<td>69.6</td>
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<td>diabetes</td>
<td>278</td>
<td>116.9</td>
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<td>infective, obstructive nephropathies</td>
<td>232</td>
<td>58.9</td>
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<td>congenital diseases</td>
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<td>0.8</td>
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<td>familial, hereditary diseases</td>
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<td>36.3</td>
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<td>polycystic kidney disease</td>
<td>106</td>
<td>35.1</td>
</tr>
<tr>
<td>toxic nephropathies</td>
<td>166</td>
<td>14.1</td>
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<td>analgesic nephropathy</td>
<td>146</td>
<td>8.8</td>
</tr>
<tr>
<td>miscellaneous conditions</td>
<td>56</td>
<td>8.6</td>
</tr>
<tr>
<td>Balkan nephropathy</td>
<td>11</td>
<td>0.4</td>
</tr>
<tr>
<td>etiology uncertain or missing</td>
<td>405</td>
<td>111.6</td>
</tr>
</tbody>
</table>

* Only in EDTA patients.
disease, parenchymal tumors (adenocarcinomas in Table 3, cancers of the kidney in Table 4) comprised about 80% of “kidney” cancers. Data from the ANZDATA and EDTA registries also indicated that transitional-cell carcinomas of the renal pelvis, ureter, or urethra were often multiple or followed bladder cancer (Tables 3 and 4).

**Trends with Time on Dialysis**

The risk of kidney cancer increased significantly with time since first dialysis in the patient population as a whole (Table 5). This significant trend of increasing risk with time was seen also in the groups of patients with arteriopathic renal diseases, glomerulonephritis, diabetes, and ESRD of unknown etiology (in EDTA, these are chiefly patients with presumed glomerulonephritis or hypertensive nephropathy but who have not had a renal biopsy); all these are categories of primary renal disease in which about 80% of kidney cancers are renal parenchymal in type. On the other hand, the excess risk of kidney cancer was highest in the first year in categories of primary renal disease associated with a relatively high proportion of urothelial cancers, namely toxic nephropathies and the sub-group of analgesic nephropathy, infective and obstructive nephropathies, and miscellaneous conditions (but not for those with Balkan nephropathy), and also in the small group of patients with congenital renal disease.

The apparent trend of decreasing risk for bladder cancer with time since first dialysis just failed to reach significance when all patients were considered together, but it was significant in the group with infective and obstructive nephropathies (Table 5). The SIR for bladder cancer were highest in the first year of dialysis for patients with toxic nephropathies and for the subgroup with analgesic nephropathy but not for those with Balkan nephropathy.

**Multivariate Analyses**

In multivariate analyses with terms fitted simultaneously for registry, gender, race (for USRDS patients only), age at first dialysis, primary renal disease, and type of dialysis, the hazard ratios (HR) for cancers of the kidney were significantly reduced for patients from EDTA compared with either ANZDATA or USRDS and for patients with diabetes as the cause of ESRD when compared with each of the other categories of primary renal disease except familial, hereditary diseases; the HR was significantly higher in patients with toxic nephropathies than in any other category of renal disease except congenital diseases (Table 6).

In respect to bladder cancer, the HR was significantly higher in ANZDATA patients and lower in EDTA patients than in those from USRDS. The HR were also higher in patients with toxic nephropathies, infective and obstructive nephropathies, and miscellaneous conditions, but they were lower in those with familial, hereditary diseases and diabetes than in each of the other categories of primary renal disease except congenital diseases, a category for which small numbers resulted in a wide confidence interval (Table 6). For neither cancer was there an effect of type of dialysis or race.

Separate multivariate analyses were performed upon the data from each registry. Patients from the United States, Europe, and Australia/New Zealand had a generally similar pattern of association of excess cancer risk with primary renal disease, some differences being apparent due to the rarity of analgesic nephropathy in the United States and the presence of Balkan nephropathy in Europe alone (Table 7).

**Discussion**

This large retrospective cohort study, drawing on population-based data from the whole of United States, Australia and
New Zealand, and much of Europe, has yielded information that helps to clarify the nature of, and excess risk for, cancers of the kidney and urinary tract in patients treated by maintenance dialysis for end-stage renal disease (ESRD). Renal parenchymal cancers are increased in all categories of primary renal disease, and the risk rises with time on dialysis treatment. On the other hand, cancers of the urinary tract are increased preeminently in those primary renal diseases that themselves are associated with urothelial tumors in the general population, and their risk does not increase with time. The relative, but not the absolute, risk for both kidney and bladder cancer is higher in younger than in older patients and in women compared with men.

The pattern of increased risk for renal parenchymal cancers in this population is consistent with an etiology related to loss of renal function and its duration, rather than to the primary renal disease or dialysis modality. Irrespective of primary renal disease, the pathologic appearance of the kidney in ESRD is dominated by changes that result directly or indirectly from loss of functional and structural integrity, tubular atrophy, interstitial inflammation, and fibrosis, arterial, arteriolar, and glomerular sclerosis, and acquired cysts. Of these, acquired renal cystic disease alone has been implicated as a risk factor for cancer (5,17).

Acquired renal cystic disease appears in both hemodialysis and peritoneal dialysis patients independently of age or primary renal disease (18); the prevalence increases with duration of dialysis (18–20), and it has been suggested that cysts may develop more quickly in men than women (20). Although this study did not examine the occurrence of acquired renal cysts, the excess incidence of renal parenchymal cancer and its increase with time could be explained by malignant degeneration.
in these cysts. An additional factor to account for the rising trend with time on dialysis is that there are fewer long-term survivors in the older age groups or among patients with diabetic nephropathy, two classes of patients that showed the least excess of kidney cancer.

No report has suggested that the prevalence of acquired renal cystic disease is related to the primary renal disease or that it is less common in diabetic nephropathy or familial, hereditary conditions (chiefly polycystic kidney disease), primary renal diseases with the least excess risk of kidney cancer. Our findings might suggest that the carcinogenic potential of acquired renal cystic disease is greater than, and may be of a different nature to, that of primary (hereditary) polycystic disease, which, on anecdotal evidence, has been implicated in the development of renal parenchymal cancer (3). Just why patients with ESRD due to diabetic nephropathy should have a relatively small excess risk of kidney cancer is not obvious.

Diabetic nephropathy progresses to ESRD more rapidly, on average, than does chronic renal failure from other common primary renal diseases, and diabetic patients have a shorter life expectancy. The excess risk of kidney cancer among diabetic patients may thus be due to other factors, such as the use of anabolic steroids.

Table 3. Characteristics of the 70 kidney cancers reported in the ANZDATA registry

<table>
<thead>
<tr>
<th>All Types</th>
<th>Adenocarcinoma</th>
<th>Transitional Cell Carcinoma</th>
<th>Other Type/Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>34 (48.6%)</td>
<td>34 (48.6%)</td>
<td>2 (2.9%)</td>
</tr>
</tbody>
</table>

Primary renal disease

<table>
<thead>
<tr>
<th>Arteriopathic renal diseases</th>
<th>5</th>
<th>4 (80.0%)</th>
<th>1 (20.0%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulonephritis</td>
<td>17</td>
<td>14 (82.4%)</td>
<td>3 (17.6%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>1 (100%)</td>
<td></td>
</tr>
<tr>
<td>Infective, obstructive nephropathies</td>
<td>6</td>
<td>4 (66.7%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>Congenital diseases</td>
<td>1</td>
<td>1 (100%)</td>
<td></td>
</tr>
<tr>
<td>Toxic nephropathies</td>
<td>34</td>
<td>6 (17.6%)</td>
<td>27 (79.4%)</td>
</tr>
<tr>
<td>Uncertain</td>
<td>6</td>
<td>4 (66.7%)</td>
<td>1 (16.7%)</td>
</tr>
</tbody>
</table>

Tumor sequence

| First primary tumors        | 48| 27 (56.3%)| 19 (39.6%)| 2 (4.2%)  |
| Second primary after bladder cancer | 9 | 2 (22.2%)| 7 (77.8%) |           |
| Second primary after other cancer | 1 | 1 (100%)  |           |           |
| Multiple primary kidney cancers | 12| 4 (33.3%)| 8 (66.7%) |           |

*a* Includes 32 with analgesic nephropathy.

*b* All bladder cancers were transitional cell.

*c* 12 primary kidney cancers in 6 patients.

Table 4. Characteristics of the 680 kidney cancers reported in the EDTA registry

<table>
<thead>
<tr>
<th>All Types</th>
<th>Wilms’ Tumor</th>
<th>Kidney</th>
<th>Renal Pelvis, Ureter/Urethra</th>
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<tr>
<td>680</td>
<td>36 (5.3%)</td>
<td>479 (70.4%)</td>
<td>165 (24.3%)</td>
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</table>

Primary renal disease

<table>
<thead>
<tr>
<th>Arteriopathic renal diseases</th>
<th>58</th>
<th>5 (8.6%)</th>
<th>48 (82.8%)</th>
<th>5 (8.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulonephritis</td>
<td>60</td>
<td>4 (6.7%)</td>
<td>51 (85.0%)</td>
<td>5 (8.4%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>33</td>
<td>2 (6.1%)</td>
<td>27 (81.8%)</td>
<td>4 (12.1%)</td>
</tr>
<tr>
<td>Infective, obstructive nephropathies</td>
<td>140</td>
<td>7 (5.0%)</td>
<td>97 (69.3%)</td>
<td>36 (25.7%)</td>
</tr>
<tr>
<td>Congenital diseases</td>
<td>3</td>
<td>3 (100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial, hereditary diseases</td>
<td>63</td>
<td>2 (3.2%)</td>
<td>50 (79.4%)</td>
<td>11 (17.4%)</td>
</tr>
<tr>
<td>Toxic nephropathies <em>a</em></td>
<td>122</td>
<td>1 (0.8%)</td>
<td>55 (45.1%)</td>
<td>66 (54.1%)</td>
</tr>
<tr>
<td>Miscellaneous conditions</td>
<td>40</td>
<td>4 (10.0%)</td>
<td>20 (50.0%)</td>
<td>15 (37.5%)</td>
</tr>
<tr>
<td>Uncertain</td>
<td>161</td>
<td>11 (6.8%)</td>
<td>127 (78.9%)</td>
<td>24 (11.1%)</td>
</tr>
</tbody>
</table>

Tumor sequence

| First primary tumor        | 637| 34 (5.3%) | 456 (71.6%) | 147 (23.1%) |
| Second primary after bladder cancer | 11| 2 (18.2%) | 2 (18.2%)  | 9 (81.8%)  |
| Second primary after other cancer | 8 | 7 (87.5%) | 1 (12.5%)  |           |
| Multiple primary kidney cancers *b* | 24| 2 (8.3%)  | 12 (50.0%) | 10 (41.7%) |

*a* Includes 110 with analgesic nephropathy.

*b* 24 primary kidney cancers in 12 patients.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Obs</th>
<th>SIR (95% CI)</th>
<th>Obs</th>
<th>SIR (95% CI)</th>
<th>Obs</th>
<th>SIR (95% CI)</th>
<th>Obs</th>
<th>SIR (95% CI)</th>
<th>Obs</th>
<th>SIR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Kidney Cancer (ICD-9 189)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all</td>
<td>632</td>
<td>3.2 (3.0 to 3.5)</td>
<td>386</td>
<td>3.1 (2.8 to 3.5)</td>
<td>630</td>
<td>3.7 (3.4 to 4.0)</td>
<td>351</td>
<td>5.0 (4.5 to 5.5)</td>
<td>54</td>
<td>6.8 (5.1 to 8.9)</td>
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<tr>
<td>arteriopathic renal diseases</td>
<td>156</td>
<td>2.7 (2.3 to 3.2)</td>
<td>97</td>
<td>2.8 (2.3 to 3.4)</td>
<td>170</td>
<td>3.8 (3.2 to 4.4)</td>
<td>88</td>
<td>5.7 (4.6 to 7.0)</td>
<td>15</td>
<td>11.4 (6.4 to 18.7)</td>
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<td>61</td>
<td>2.7 (2.1 to 3.5)</td>
<td>51</td>
<td>3.5 (2.6 to 4.5)</td>
<td>85</td>
<td>3.9 (3.1 to 4.8)</td>
<td>63</td>
<td>6.6 (5.1 to 8.5)</td>
<td>12</td>
<td>11.4 (5.9 to 20.0)</td>
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<tr>
<td>diabetes</td>
<td>105</td>
<td>2.1 (1.7 to 2.6)</td>
<td>63</td>
<td>2.2 (1.7 to 2.9)</td>
<td>82</td>
<td>2.6 (2.1 to 3.2)</td>
<td>27</td>
<td>3.8 (2.5 to 5.5)</td>
<td>1</td>
<td>2.9 (0.0 to 15.9)</td>
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<tr>
<td>infective, obstructive nephropathies</td>
<td>83</td>
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<td>3.6 (2.6 to 4.9)</td>
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<td>3.6 (2.5 to 5.0)</td>
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<td>0.0 (0.0 to 22.3)</td>
<td>2133</td>
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<tr>
<td>familial, hereditary diseases</td>
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<td>3.4 (2.3 to 4.8)</td>
<td>23</td>
<td>3.5 (2.2 to 5.2)</td>
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<td>2.7 (1.8 to 3.7)</td>
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<td>2.8 (1.8 to 4.3)</td>
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<td>0.9 (0.0 to 5.1)</td>
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<td>3.6 (2.3 to 5.4)</td>
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<td>2.7 (1.9 to 3.9)</td>
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<td>toxic nephropathies</td>
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<td>12.5 (8.7 to 17.4)</td>
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<td>8.4 (6.0 to 11.5)</td>
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<td>9.5 (6.0 to 14.3)</td>
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<td>3.6 (0.0 to 19.9)</td>
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<td>5.1 (2.7 to 8.8)</td>
<td>8</td>
<td>5.8 (2.5 to 11.3)</td>
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<td>4.9 (3.9 to 6.0)</td>
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<td>489</td>
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<td>1.4 (0.3 to 4.0)</td>
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<td>1.3 (0.9 to 1.8)</td>
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<td>13.6 (9.0 to 19.6)</td>
<td>53</td>
<td>13.9 (10.4 to 18.2)</td>
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<td>8.0 (4.6 to 13.1)</td>
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<td>0.75</td>
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<td>2.7 (1.5 to 4.4)</td>
<td>8</td>
<td>2.1 (0.9 to 4.2)</td>
<td>21</td>
<td>3.8 (2.4 to 5.9)</td>
<td>8</td>
<td>2.7 (1.1 to 5.3)</td>
<td>1</td>
<td>2.3 (0.0 to 12.9)</td>
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<td>Balkan nephropathy</td>
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<td>17.6 (3.5 to 51.6)</td>
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<td>13.0 (2.6 to 38.1)</td>
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<td>0</td>
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<tr>
<td>etiology uncertain or missing</td>
<td>107</td>
<td>1.5 (1.2 to 1.8)</td>
<td>68</td>
<td>1.5 (1.1 to 1.9)</td>
<td>85</td>
<td>1.2 (1.0 to 1.5)</td>
<td>34</td>
<td>1.0 (0.7 to 1.4)</td>
<td>5</td>
<td>1.0 (0.3 to 2.4)</td>
</tr>
</tbody>
</table>

* Using the Wilcoxon-Mann-Whitney test. Figures represent numbers of observed cancers (Obs), standardized incidence ratios (SIR), and confidence intervals (95% CI).
expectancy when on dialysis; therefore, a plausible explanation is that the apparent protection is due in part to the shorter duration of exposure to chronic renal failure (predialysis plus dialysed) of diabetic patients when compared with the experience of the majority of patients with ESRD due to other causes.

Although there was no association of primary renal disease with excess risk for cancer of the renal parenchyma (except perhaps some protection afforded by diabetes), an association with primary renal disease accounts for much, possibly all, of the excess risk of urothelial cancer, whether in the bladder or elsewhere in the urinary tract as denoted by transitional cell carcinomas of the kidney (in ANZDATA) or cancers of the renal pelvis, ureter, or urethra (in EDTA). Although there was no excess risk of bladder cancer associated with diabetes or familial, hereditary diseases on the one hand, patients with analgesic or Balkan nephropathy, diseases strongly associated with carcinogenesis throughout the urinary tract (2,4,21,22), had more than ten times the general risk. Patients with infective or obstructive nephropathies also exhibit a relatively high SIR in the dialysis population as well as an excess risk for urothelial cancer in the general population (23,24). We are unable to shed further light on the especially high risk of cancers of both kidney and bladder seen in the smallest group of patients, those with congenital renal diseases, as most of the cases were from the United States, for which we have no histologic or sub-site classification. The small excess risks of bladder cancer associated with arteriopathic renal diseases and glomerulonephritis, diabetes might be explained by the association of these primary renal diseases with tobacco and cytotoxic treatment (e.g., cyclophosphamide), respectively.

With regard to the categorization of primary renal diseases, the number of diagnoses and variations in diagnostic practice between and within countries necessitates grouping before analysis. Least controversial are those groupings (arteriopathic renal disease, glomerulonephritis, diabetes) that include cases with a general diagnosis, based upon agreed and easily applied clinical criteria, together with those with the same renal disease but a more specific diagnosis on the basis of histology or imaging. For these primary renal disease categories, there is likely to be good agreement among nephrologists from the same country, but between countries or racial groups, the choice of diagnosis for those cases without histologic or imaging proof will be influenced by current local perceptions (25). The grouping for which there appeared to be least concordance between the registries was infective, obstructive nephropathies, covering diseases of the kidney that result from abnormality or pathology in the urinary tract. USRDS records the largest number of patients in this classification as chronic interstitial nephritis, EDTA as pyelonephritis, and ANZDATA as reflux nephropathy, each believed to comprise chiefly renal disease caused by primary vesicoureteral reflux, although, at least in Europe, pyelonephritis probably includes some analgesic nephropathy (14). Despite this lack of uniformity, we found similar excess risks for cancer across all three registries for infective, obstructive nephropathies, covering diseases of the kidney that result from abnormality or pathology in the urinary tract.

Table 6. Multivariate analysis (COX): combined data from all three registries

<table>
<thead>
<tr>
<th>Variable</th>
<th>Kidney Cancer (ICD-9 189) HR (95% CI)</th>
<th>Bladder Cancer (ICD-9 188) HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANZDATA (Australia, New Zealand)</td>
<td>1.17 (0.90 to 1.53)</td>
<td>1.44 (1.07 to 1.94)</td>
</tr>
<tr>
<td>EDTA (Europe)</td>
<td>0.55 (0.49 to 0.61)</td>
<td>0.79 (0.71 to 0.89)</td>
</tr>
<tr>
<td>USRDS (United States)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Primary renal disease</td>
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<td></td>
</tr>
<tr>
<td>arteriopathic renal diseases</td>
<td>1.21 (1.04 to 1.40)</td>
<td>1.11 (0.93 to 1.32)</td>
</tr>
<tr>
<td>glomerulonephritis</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>diabetes</td>
<td>0.71 (0.60 to 0.85)</td>
<td>0.60 (0.48 to 0.74)</td>
</tr>
<tr>
<td>infective, obstructive nephropathies</td>
<td>1.42 (1.19 to 1.70)</td>
<td>2.37 (1.97 to 2.86)</td>
</tr>
<tr>
<td>congenital diseases</td>
<td>2.09 (1.11 to 3.94)</td>
<td>2.33 (1.03 to 5.28)</td>
</tr>
<tr>
<td>familial, hereditary diseases</td>
<td>0.83 (0.66 to 1.04)</td>
<td>0.62 (0.46 to 0.85)</td>
</tr>
<tr>
<td>toxic nephropathies</td>
<td>4.40 (3.57 to 5.41)</td>
<td>5.65 (4.53 to 7.04)</td>
</tr>
<tr>
<td>miscellaneous</td>
<td>1.99 (1.49 to 2.66)</td>
<td>2.52 (1.86 to 3.42)</td>
</tr>
<tr>
<td>uncertain</td>
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<td>1.13 (0.94 to 1.37)</td>
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<tr>
<td>Type of dialysis</td>
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<td></td>
</tr>
<tr>
<td>hemodialysis</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>mixed</td>
<td>1.05 (0.93 to 1.18)</td>
<td>0.83 (0.71 to 0.96)</td>
</tr>
<tr>
<td>peritoneal</td>
<td>0.84 (0.68 to 1.04)</td>
<td>0.87 (0.70 to 1.07)</td>
</tr>
<tr>
<td>unknown</td>
<td>0.88 (0.68 to 1.14)</td>
<td>0.97 (0.73 to 1.29)</td>
</tr>
</tbody>
</table>

* Hazards ratios (HR) and 95% confidence intervals (CI) obtained from COX proportional hazards regression models with all terms (registry, gender, race, age at first dialysis, primary renal disease, and type of dialysis) fitted simultaneously.
phropathy; miscellaneous) will vary between and within registries according to (1) the regional prevalence of certain diseases (notably analgesic nephropathy in Australia, Balkan nephropathy in SE Europe), and (2) prevailing clinical practice, being higher where diagnosis is pursued more vigorously, as is understood to be the case in Australia and New Zealand; ANZDATA is the registry with the lowest percentage of patients with unknown or uncertain diagnosis (6.6% versus 12.2% for USRDS and 29.8% for EDTA) or with glomerulonephritis without the histologic type being identified (33% versus 47% for EDTA and 63% for USRDS) (14).

In the dialysis population, the excess risks for cancers of the kidney and bladder, like those for cancer at all sites (1), are relatively (although not absolutely) greater at younger ages, and more in women than men, a pattern also seen in ESRD patients with kidney transplants (26,27). This suggests that cancer risk factors acting specifically in the renal dialysis and transplantation populations are a good deal less dependent on age, as well as being decidedly more potent, than the risk factors that account for most cancers in the general population.

As patients with ESRD cannot survive for any length of time without dialysis or transplantation, it is not possible to separate the effect upon cancer risk of prolonged loss of kidney function from that of these treatments without collateral evidence. Although no comprehensive formal comparison has been undertaken, the increased risk for cancer appears to be greater in recipients of kidney grafts than in the dialysis population (27,28), signifying that transplantation itself confers some additional cancer risk. Akizawa et al. (10) suggested that blood membrane interactions, specific to hemodialysis, might be carcinogenic, but no more conclusive observations have been published. Moreover, as hemodialysis and peritoneal dialysis expose the patient to a dissimilar range of foreign, potentially bioincompatible materials and solutions, the absence of a significant difference in the risks conferred according to dialysis modality for cancers of the kidney (except in ANZDATA) or

### Table 7. Multivariate analysis (COX): data from each registry considered separately

<table>
<thead>
<tr>
<th>Variable</th>
<th>ANZDATA (AUS, NZ) HR (95% CI)a</th>
<th>EDTA (Europe) HR (95% CI)b</th>
<th>USRDS (United States) HR (95% CI)b</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kidney cancer (ICD9-189)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>primary renal disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>arteriopathic renal diseases</td>
<td>1.0 (0.4 to 2.8)</td>
<td>1.1 (0.7 to 1.5)</td>
<td>1.2 (1.0 to 1.5)</td>
</tr>
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<td>glomerulonephritis</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>diabetes</td>
<td>0.2 (0.0 to 1.3)</td>
<td>0.7 (0.4 to 1.0)</td>
<td>0.8 (0.6 to 0.9)</td>
</tr>
<tr>
<td>infective, obstructive nephropathies</td>
<td>1.4 (0.6 to 3.6)</td>
<td>1.5 (1.1 to 2.1)</td>
<td>1.3 (1.0 to 1.7)</td>
</tr>
<tr>
<td>congenital diseases</td>
<td>0.8 (0.3 to 2.7)</td>
<td>4.2 (2.0 to 9.0)</td>
<td>4.2 (2.0 to 9.0)</td>
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<td>familial, hereditary diseases</td>
<td>1.0 (0.7 to 1.4)</td>
<td>0.8 (0.6 to 1.1)</td>
<td>0.8 (0.6 to 1.1)</td>
</tr>
<tr>
<td>toxic nephropathy</td>
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<td>5.2 (3.8 to 7.2)</td>
<td>1.6 (0.8 to 3.0)</td>
</tr>
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<td>1.5 (1.2 to 1.8)</td>
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<tr>
<td>hemodialysis</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
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<td>mixed</td>
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<td>1.0 (0.9 to 1.2)</td>
</tr>
<tr>
<td>peritoneal</td>
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<td>0.9 (0.6 to 1.2)</td>
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<td><strong>Bladder cancer (ICD9-188)</strong></td>
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<td>primary renal disease</td>
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<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
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<td>0.5 (0.3 to 0.8)</td>
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<tr>
<td>toxic nephropathy</td>
<td>6.0 (2.7 to 13.5)</td>
<td>9.9 (6.5 to 14.9)</td>
<td>1.9 (1.1 to 3.5)</td>
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<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
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<td>0.7 (0.5 to 1.0)</td>
<td>0.8 (0.7 to 1.0)</td>
</tr>
<tr>
<td>peritoneal</td>
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<td>0.9 (0.6 to 1.2)</td>
<td>1.0 (0.7 to 1.3)</td>
</tr>
<tr>
<td>unknown</td>
<td></td>
<td></td>
<td>1.0 (0.7 to 1.3)</td>
</tr>
</tbody>
</table>

*a Hazards ratio (HR) and 95% confidence intervals (CI) obtained from COX proportional hazards regression models with all terms for age, gender, race, age at first dialysis, primary renal disease, and type of dialysis fitted simultaneously.

b Also adjusted for race.
bladder in this study, and for cancers at all sites in our earlier publication (1), suggest that dialysis itself confers no additional risk for cancer other than by prolonging exposure to the uremic state. Finally, the different pattern of increased risk demonstrated for cancers of the kidney on the one hand and bladder on the other in patients similarly exposed to dialysis suggests a nondiabetic etiology. However, an effect common to and of about equal potency in hemodialysis and peritoneal dialysis cannot be ruled out.

In the multivariate analysis, ANZDATA patients show a significantly higher risk of bladder cancer than those from USRDS or EDTA. This is explained by the lower incidence of bladder cancer in the general population of Australia and New Zealand than in the United States or Europe (15,16); with the same absolute risk, the SIR will be inversely proportional to the underlying rate. The lower risks recorded for both cancers by EDTA are due chiefly to underreporting by clinicians from some countries, as SIR calculated for European countries known to have high-quality cancer data were similar to those for ANZDATA (1). When data from the three registries was considered separately, smaller numbers reduced statistical power, especially in the ANZDATA set, so that fewer differences reached significance; on the other hand, trebling the number of comparisons also trebled the likelihood of showing “statistically significant” differences by chance. Moreover, it should be noted that the three HR in any one row of Table 7 cannot be compared directly, as the HR for each registry is calculated in relation to its own, not a common, reference category.

As with any large data set derived from reporting by individual clinicians, errors and incomplete recording are likely. Recording errors will be a source of bias only if the reporting of cancer is consistently either more or less complete or correct to the dialysis registry than to the corresponding population-based cancer registry. A quality-control audit was conducted on all patients treated by dialysis in the Australian state of New South Wales (NSW) by two of the authors. Of 241 cancers notified to one or other registry, 201 were reported to both (with only one major and 16 minor differences in coding, and 8 with dates of diagnosis that differed by more than 3 mo), 27 to the NSW Central Cancer Registry alone, and 13 only to ANZDATA. Thus, in this sample, the dialysis registry recorded 6% fewer cancers than the reference cancer registry. An English survey also found underrecording of cancer in transplant recipients, to a greater extent by the transplant registry than by the regional cancer registry (29). As the SIR were generally higher in ANZDATA patients than those from the other registries, this audit implies there was some underrecording of cancer incidence by all three dialysis registries.

A partial explanation for the disproportionate excess of cancers of the urinary tract in the first year of dialysis may be detection bias resulting from the diagnostic work-up associated with starting dialysis. However, in patients with ESRD, nephrologists would be rather more likely to perform upper abdominal imaging, which would reveal occult renal parenchymal cancers (which did not show an excess in the first year of dialysis), than urinary cytology by which asymptomatic urinary cancers would be discovered. For this reason, we believe a more probable explanation for the excess of urinary cancers in the first year of dialysis is registration practice in respect of patients with a chronic kidney disease (e.g., analgesic nephropathy) in which the final loss of renal function resulted from a previously undetected urothelial cancer. In some such cases, preference may have been given to recording the underlying kidney condition, not the cancer, as the primary renal disease.

It has been suggested that the relative deficit of cancers at all sites in older or diabetic dialysis patients is explained by “competing risks” resulting from their higher mortality from other causes (30,31). In the dialysis population, competing risks are not only common (e.g., death from nonrenal disease or failure to enter dialysis treatment in the predialysis period, and non-cancer death or transplantation in the dialysis period), but also are unevenly distributed, associated as they are with age, primary renal disease, and country where dialysed. Kaplan-Meier plots do not correct for errors introduced by competing risks; they are included in this article only for illustrative purposes. When SIR are used, the effect of competing risks would be little if any greater on the numerator (number of patients with cancer) than on the denominator (number of patients at risk); hence our reliance on this statistic. Because of their reduced life expectancy, older or diabetic patients, however, are likely to be subject to less surveillance, a source of negative detection bias.

We believe none of these biases or errors is of sufficient magnitude to vitiate our major findings.

This dialysis population exhibited a risk of cancers of the kidney and urinary tract over and above the heightened risk for cancer seen at many other sites. The excess risk was attributed to factors that differed for renal parenchyma and urothelium. Nonspecific change within the kidney resulting from loss of renal function suggested to be acquired renal cystic disease, is the putative risk factor for the excess of renal parenchymal cancers that was seen independently of primary renal disease and increased in frequency with advancing duration of dialysis. On the other hand, an association with certain primary renal diseases accounted for much, or possibly all, of the heightened incidence of cancers of the bladder and upper urinary tract, a risk that remained constant (or perhaps fell) with time after starting dialysis. The absence of a significant difference according to dialysis modality made it unlikely that dialysis itself was responsible. Contrary to expectation, there was no undue excess risk of kidney cancer in patients with ESRD due to polycystic kidney disease.

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References


