The pattern of excess cancer in dialysis and transplantation

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Abstract

Background. After transplantation, cancer risk varies from no increase for several common cancers to a many-fold increase for a number of, chiefly virus-associated, cancers. The smaller excess of cancer in dialysis has been less well described, but two studies suggested that impaired immunity might be responsible.

Methods. In a population-based cohort study of 28 855 patients who received renal replacement therapy (RRT), we categorized incident cancers as end-stage kidney disease (ESKD) related, immune deficiency related, not related to immune deficiency, or of uncertain status, according to whether they were, or were not, increased in published reports of cancer in ESKD prior to starting RRT, organ
transplantation or human immunodeficiency virus infec-
tion. Standardized incidence ratios for, and excess burdens of, cancer were calculated for all persons normally resident in Australia starting treatment by dialysis or renal transplantation from 1982 to 2003.

**Results.** The risk for ESKD-related cancers was increased 4-fold in dialysis and during transplant function. For immune deficiency-related cancers, the increase was 1.5 (95% CI 1.3–1.6) times in dialysis, and 5-fold after transplantation. ESKD- or immune deficiency-related cancers contributed to ~90% of the excess burden of cancer, 48% and 36%, respectively, in dialysis, and 10% and 78% after transplantation. The remaining excess malignancy was contributed by cancers whose relationship with ESKD and immune deficiency is not yet certain.

**Conclusions.** In RRT, the increase in cancer is restricted, largely if not wholly, to cancers with origins in ESKD or related to immune deficiency. For the former, the cancer risk is similar in dialysis and transplantation, but for immune deficiency-related cancers, the relative risk is much greater after transplantation.

**Keywords:** cancer; dialysis; end-stage kidney disease; immune deficiency; renal transplantation

**Introduction**

The patients on renal replacement therapy (RRT) are at increased risk of cancer whether treated by dialysis or transplantation. However, the magnitude of the increase and the pattern of risk differ according to RRT modality, overall risk being higher after transplantation due chiefly to an excess of virus-associated cancers [1]. Prior to our recent analysis [1], the cancer risk in dialysis had been ascertained from studies with small numbers [2] or subject to ascertainment bias because cancers were identified from ESKD registries, not population-based cancer registries, and possibly some errors may have occurred as the numbers of expected cases were calculated from rates obtained from regional or neighbouring national registries for those countries not covered by a national cancer registry [3]. With regard to the cancer risk after transplantation, all five population-based retrospective cohort studies that identified incident cancers through cancer registries included the follow-up of patients from the date of first transplantation until diagnosis of cancer or death, but follow-up was not censored at the time of graft failure and return to dialysis [1,4–7]. In one cohort study, 16% of patients had received a transplant of an organ other than kidney [6]. For this analysis, we have used data from a single population-based study to calculate risks of cancer during dialysis prior to first transplantation and during the function of a first renal transplant.

The pattern of cancer risk in transplant recipients resembles that in persons with human immunodeficiency virus (HIV) infection, in whom the increased risk also stems predominantly, but not exclusively, from cancers with viral aetiology. Impaired immunity is thought to be principally responsible for this association [8,9]. However, there are notable differences between the cancer profiles in these two immune-deficient populations, chiefly pertaining to five cancers that are increased in transplant recipients but not, or by much less, in HIV [8]. For four of these cancers (kidney, urinary tract, thyroid, myeloma), the risk is as high in persons with end-stage kidney disease (ESKD) prior to starting RRT, and in those treated by dialysis, as it is after transplantation [1], indicating that the risk antedates pharmacological immunosuppression. Accordingly, we have categorized these four cancers as ‘ESKD related’ (Table 1).

In this paper, we estimate the proportion of excess malignant disease contributed by cancers related to ESKD or to immune deficiency in dialysis and renal transplantation, and determine whether these two broad categories account for the whole additional burden of cancer in RRT.

**Patients and methods**

Ethical approval was given by all 10 registries from whom we obtained data. The study team had access only to data from which all personal identification had been removed.

**Study cohort**

The Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) records all patients treated by long-term RRT in either country by date of birth, sex, primary renal disease and type of treatment [10]. We included persons normally resident in Australia who started RRT by dialysis, or who had their first renal transplant, between 1 January 1982 and 30 September 2003.

The dialysis cohort comprised all persons treated by dialysis up to the time of receiving their first transplant, and the transplant cohort all persons throughout the period of function of their first transplant. Study participants were censored at death, on the date cancer registry records were no longer available (31 December of 2001, 2002 or 2003 depending on the state or territory of cancer registration), when lost to follow-up (n = 93, 1.1%), when transplanted (for persons on dialysis) or at graft failure (for transplant recipients) and, for each cancer site, from the date of diagnosis of the first cancer at that site (whether before or after starting RRT).

We excluded cancers deemed to have been present prior to starting RRT, including those diagnosed during dialysis when that cancer had been recorded by ANZDATA as being directly or indirectly the cause of ESKD (prostate: n = 6; NHL: n = 2; immunoproliferative disease: n = 1; unspecified primary site: n = 1). Independent perusal of ANZDATA records had indicated that reporting of myeloma to cancer registries was frequently delayed in persons commencing dialysis, seemingly because myeloma can be diagnosed without a histopathology report or hospital admission, the means by which cancer registries are usually notified. Examination of our data indicated that myeloma incidence was greater throughout the first 2 years of dialysis than in persons who were on dialysis beyond that time; accordingly we excluded the first 2 years of dialysis when calculating the SIR for this cancer.

**Ascertainment of cancers**

Throughout Australia, all cancers (other than non-melanocytic skin cancer) in persons normally resident in Australia must, by law, be reported by the histopathologist and by the treating doctor or hospital to the relevant state (n = 6) or territory (n = 2) cancer registry, which transmits records of all registered cancers to the National Cancer Statistics Clearing House (NCSCH). Incident primary cancers in the study cohort were identified by linkage with NCSCH records using an established probabilistic matching technique [1,11]. Second and subsequent cancers at any one site were excluded.

For the calculation of expected numbers of cancers, incidence rates by site, age in 5-year groups, sex and state or territory of residence were obtained for all Australians for each year from 1982 to 2001, with rates for 2001 being used for later years.
Table 1. Categorization of cancers in the end-stage kidney disease (ESKD) population

<table>
<thead>
<tr>
<th>Category</th>
<th>Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESKD related</td>
<td>Kidney (C64), Urinary tract (C65–68), Thyroid (C73), Myeloma (ICD-O3 9731–9734)</td>
</tr>
<tr>
<td>Not related to immune deficiency</td>
<td>Rectum (C19–20), Breast (C50), Ovary (C56), Prostate (C61)</td>
</tr>
</tbody>
</table>

Statistical analysis
The ratio of observed to expected numbers of cancers, the standardized incidence ratio (SIR), was estimated with exact Poisson 95% confidence intervals (CIs) using Stata version 8 (Stata Corp LP, College Station, TX, USA). The additional burden of cancer was calculated from the difference between the observed and expected numbers of cancers, per 100 000 person years at risk.

Categorization of cancer
Cancers were grouped according to whether they were, or were not, related to ESKD or immune deficiency by criteria based on recent publications [1,8] (Table 1). Cancers were deemed to be related to ESKD when a more than 2-fold risk in persons with ESKD prior to starting RRT [1] was associated with no (urinary tract, thyroid), or a much smaller (kidney, myeloma), excess risk in persons with HIV [8]. All other cancers were grouped as being, or not being, related to immune deficiency if the cancer in question was increased, or not increased, in persons with HIV as well as in transplant recipients [8]. The remaining cancers were categorized as ‘of uncertain status’. No cancer was excluded, or included in more than one category.

Results
The study population is described in Table 2. Persons on dialysis were, on average, older and slightly less likely to be male than transplant recipients. There were nearly three times as many persons in the dialysis cohort, but the mean duration of follow-up was more than twice as long after transplantation (6.0 years) than for persons on dialysis (2.7 years). The mean duration of dialysis prior to transplantation was 2.0 years (standard deviation 2.0 years); and the median duration was 1.4 years (inter-quartile range 0.6–2.8 years). For the 8173 recipients of a first transplant, the immunosuppressive regimen was known for 48 079 (97.4%) person years of observation. It included azathioprine and/or mycophenolate without a calcineurin inhibitor for 21% of person years; azathioprine and/or mycophenolate...
Table 3. Risk of cancer during dialysis (prior to any transplantation) or during the period of function of the first kidney transplant, by cancer category

<table>
<thead>
<tr>
<th>Cancer type/site (ICD-10/ICD0–3)</th>
<th>Dialysis</th>
<th>Transplantation</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>O&lt;sup&gt;b&lt;/sup&gt;</td>
<td>E&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>All cancers&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1018</td>
<td>702</td>
</tr>
<tr>
<td>Related to ESKD</td>
<td>215</td>
<td>49.6</td>
</tr>
<tr>
<td>Kidney (C64)</td>
<td>82</td>
<td>15.2</td>
</tr>
<tr>
<td>Urinary tract (C65–C68)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>88</td>
<td>25.8</td>
</tr>
<tr>
<td>Renal pelvis (C65)</td>
<td>25</td>
<td>2.5</td>
</tr>
<tr>
<td>Bladder (C67)</td>
<td>58</td>
<td>22.1</td>
</tr>
<tr>
<td>Thyroid (C73)</td>
<td>37</td>
<td>4.2</td>
</tr>
<tr>
<td>Myeloma (9731–9734)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>5</td>
<td>2.8</td>
</tr>
<tr>
<td>Not related to ESKD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune deficiency related&lt;sup&gt;f&lt;/sup&gt;</td>
<td>382</td>
<td>258</td>
</tr>
<tr>
<td>Not related to immune deficiency&lt;sup&gt;f&lt;/sup&gt;</td>
<td>186</td>
<td>224</td>
</tr>
<tr>
<td>Cancers of uncertain status&lt;sup&gt;f&lt;/sup&gt;</td>
<td>235</td>
<td>171</td>
</tr>
</tbody>
</table>

<sup>a</sup>International Classification of Diseases, 10th revision; International Classification of Diseases for Oncology, 3rd Edition.
<sup>b</sup>O, observed number of cancers; E, expected number of cancers; risk of cancer, given by the standardized incidence ratio (SIR), with 95% confidence interval (CI).
<sup>c</sup>Excluding non-melanocytic skin cancers.
<sup>d</sup>Also includes cases of cancer of ureter (C66) or other and unspecified urinary tract (C68).
<sup>e</sup>See the text in the ‘Results’ section for estimates of relative risk for myeloma in dialysis.
<sup>f</sup>See Table 1 for categorization of cancers that are not related to ESKD.

As shown in Figure 1, the excess of cancer during transplant function (1046 per 100 000 person years) was just over twice that in dialysis (491 per 100 000 person years). During dialysis, 48% (representing 261 cancers per 100 000 person years) of the additional burden was contributed by ESKD-related cancers and 36% (196 cancers per 100 000 person years) by immune deficiency-related cancers. During transplant function, immune deficiency-related cancers accounted for 78% (representing 838 cancers per 100 000 person years) and ESKD-related cancers for 10% (109 cancers per 100 000 person years) of the excess malignancy. In both RRT modalities, there was a deficit (not statistically significant; Table 3) of cancers not related to immune deficiency. The contribution from cancers of

Fig. 1. The burden of excess cancers by cancer category and type of renal replacement therapy.
having been exposed to all the risk factors associated with kidney pathology. Kidney transplant recipients, in addition to but it does prolong pre-RRT carcinogenic exposures since it neither fully replaces renal function nor reverses kidney pathology. Kidney transplant recipients, in addition to having been exposed to all the risk factors associated with ESKD and (usually) dialysis, receive anti-rejection drugs that profoundly suppress immunity and may themselves be carcinogenic [15].

Each of the ESKD-related cancers is linked to renal failure in a different way. Kidney cancer is chiefly a consequence of acquired cystic kidney disease [12,14] that is present in ~40% of graft recipients when transplanted, and appears after transplantation in a further 16% [Goh et al., Transplantation 2008; 86 (Suppl 2S): 100], explaining the continuing high risk for kidney cancer in transplant recipients. Whether kidney cancer is also increased by immune deficiency is not yet certain. In the meta-analysis by Grulich et al. [8], the risk for kidney cancer in persons with HIV was raised (SIR 1.5, 95% CI 1.2–1.8), but this analysis has been recently updated with new US data, the revised meta-SIR estimate being 1.3 (95%CI 1.1–1.6) [16].

Several diseases that cause ESKD are themselves risk factors for urinary cancers, particularly of the renal pelvis, and these may appear after starting RRT [12]. Chief among these is analgesic nephropathy, which has been common in Australia. More generally, the reduction or absence of urinary flow may increase the risk of urinary cancer [14]. Bladder and ‘other urinary tract’ cancers are not increased in HIV [8,16], and so are unlikely to be related to immune deficiency.

It has been suggested that the increase in thyroid cancer stems from reduced production of the selenocysteine-containing enzyme, glutathione peroxidase, either from damage to proximal tubular epithelium, the chief source of the circulating form of the enzyme, or from uraemia-related selenium deficiency [13]. Glutathione peroxidase is an important free radical scavenger, particularly in the thyroid gland. Thyroid cancer rates generally have been higher during dialysis and after transplantation than before starting RRT [1,4–7]. There is no increase of thyroid cancer in patients with HIV [8], making a contribution from immune deficiency unlikely. Detection bias may have occurred from imaging in patients with hyperparathyroidism but, as 8 of 23 thyroid cancers in Australian transplant recipients had spread to lymph nodes at diagnosis [17], the increase does include clinically significant cancers.

Although myeloma fulfils the criteria for inclusion in the group of immune deficiency-related cancers [8], it has been classified as ESKD related for this analysis as it, or its precursors, may cause ESKD independently of pre-existing kidney disease. This accounts for the exceptionally high risk of myeloma in the 5 years before starting RRT [1]. By excluding from this analysis, 68 cases of myeloma diagnosed within 2 years of starting dialysis on the presumption that some had caused ESKD, the SIR for myeloma in dialysis was reduced from the previously reported 9.6 (95%CI 7.6–11.9) [1] to 1.9 (95%CI 0.8–3.6). This more conservative SIR is likely to represent the true relative risk of myeloma conferred by being on dialysis, independently of the contribution from myeloma as a cause of ESKD.

Although we have categorized cancers that are increased both in transplant recipients and persons with HIV as ‘immune deficiency related’, disproportionately high exposure to oncogenic virus infection may account for some of the excess cancer in both populations, from blood transfusion.
and transmission in the grafted organ on the one hand, and by sexual transmission or blood contamination on the other. In particular, patients on RRT commonly were exposed to hepatitis B and C before screening tests for these viruses and treatment with erythropoietin were introduced, for hepatitis B in 1970 [18], and for hepatitis C and erythropoietin in the 1980s [19]. As it happens, the risk for liver cancer is not particularly high in dialysis (SIR 2.2, 95% CI 1.2–3.7) or after transplantation (SIR 1.0) compared with other cancers related to immune deficiency, and our findings would be unchanged if liver cancer were taken out of the group of immune deficiency-related cancers. Moreover, there is independent evidence that immune deficiency contributes to the risk for liver cancer in HIV [20]. The risk for three of the more common immune deficiency-related cancers, lip cancer [21], non-Hodgkin lymphoma [22] and melanoma [23] has been shown to decline significantly when immunosuppressive drugs are withdrawn after graft failure and return to dialysis, providing direct evidence for the role of immune deficiency in these particular cancers.

In the pre-RRT population, three (non-Hodgkin lymphoma, Kaposis sarcoma and lip cancer) of the eight cancers at increased risk [1] are immune deficiency related, one (colon cancer) is of uncertain status, and the other four form the group of ESKD-related cancers. The risk of immune deficiency-related cancer in the pre-RRT population, calculated from data published in Vajdic et al. [1], was raised slightly (SIR 1.17, 95% CI 1.02–1.32). On the whole, these data support the view that immune deficiency contributes to the excess cancer risk in patients with ESKD prior to starting RRT and, more certainly from the present analysis, in persons treated by dialysis.

For completeness, we included cancers whose relationship with immune deficiency and to ESKD is not yet certain, but this is a heterogeneous group from which conclusions should not be drawn. Accordingly, we did not give SIRs for this cancer category. Of the two most common cancers ‘of uncertain status’, cancers with no specified primary site almost certainly include many ESKD- and immune deficiency-related cancers, while colon cancer is not increased in HIV [8], and therefore is unlikely to be immune deficiency related. The rest are relatively uncommon cancers for which published data are not yet sufficient to be sure of their status.

In RRT, whether by dialysis or transplantation, the relative risk, but not the absolute risk, generally was greater in younger than in older persons, for all cancers, for the group of cancers associated with impaired immunity, and for two of the ESKD-related cancers (kidney and urinary tract), confirming previous reports [3,4,6,7,12,24]. There is no straightforward explanation for this finding [14]. It may reflect that dialysis and transplantation both simply add to the cancer risk, thus raising the SIR more when the denominator is smaller, as in younger persons. An alternative explanation, that dialysis and transplantation in some way remove the protection against cancer afforded by youth, seems incompatible with the absence of an increased risk in either dialysis or transplantation for several common cancers, comprising the group designated ‘unrelated to immune deficiency’, for which youth bestows manifest protection in the normal population.

The effect of age must be taken into consideration when comparing findings in dialysis patients who have not been transplanted, with transplant recipients who are largely a subset of the dialysis population selected on the basis of a kidney donor being available and medical suitability for transplantation. The latter depends largely on comorbidity, which is correlated with age as well as with (non-age related) cancer risk factors, for example, smoking. Part of the higher relative cancer risk in transplant recipients in this study is explained by their age being, on average, some 11 years younger (12.6 years younger on entry to treatment, less ∼1.6 years for difference in the mean duration of follow-up, from Table 2) than in persons on dialysis.

As all patients on RRT are under close medical surveillance encompassing, inter alia, organ imaging from time to time and some screening for asymptomatic cancer, inevitably lead-time bias will have resulted in earlier diagnosis and some increase in cancer incidence. The effect would have been greatest when medical supervision was most intense, for example on starting RRT, when being assessed for transplantation, and for a time after transplantation. On the other hand, screening for asymptomatic cancer may have been less diligent in poor prognosis dialysis patients than in the general population. Cancers most likely to be affected by lead-time bias include three of the four that are not increased in RRT (breast, prostate, rectum), cancers of the cervix and colon, and those such as kidney and lung cancer that may be detected incidentally by imaging. Another effect of increased pre-transplant surveillance will have been to preferentially exclude from transplantation patients at high risk of cancer, thereby reducing its incidence after transplantation.

Incipient ESKD selectively confers an increased risk of cancer, substantial in the case of thyroid, kidney and urinary tract, but small in respect of immune deficiency-related cancers. These risks persist, and may increase, during dialysis treatment. After transplantation, the excess risk for cancer is restricted to categories that show some increase in dialysis: the immune deficiency-related cancers that rise many fold, and the ESKD-related cancers that show no further increase.

Acknowledgement. We acknowledge the diligence with which dialysis and transplantation units throughout Australia have regularly submitted the information on which this analysis has been performed, and the commitment of the ANZDATA staff who have created and maintained the database so accurately. We thank the state and territory cancer registries for use of their data, and the Australian Institute of Health and Welfare and the Cancer Council of Victoria for their assistance in the conduct of this study. This work was supported by the Cancer Council of NSW (RG 47/03); the National Health and Medical Research Council (ID 510346 to CV, ID 401131 to MvL) and the Cancer Institute of New South Wales (07/CDF/1-38 to CV, 06/RSA/1/28 to MvL). The ANZDATA Registry office is supported by the Australian Department of Health and Ageing, the New Zealand Ministry of Health and Kidney Health Australia.

Conflict of interest statement. None declared.

References

Incidence of Merkel cell carcinoma in renal transplant recipients

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Abstract

Background. The risk factors for Merkel cell carcinoma (MCC), a rare type of skin cancer, are poorly understood. Some evidence suggests that MCC is more common in individuals with abnormal immune function resulting from viral infection, autoimmune disease or organ transplantation.

Methods. The national Renal Transplant Registry and the Finnish Cancer Registry data were searched for recipients of a renal transplant who were diagnosed with MCC. The MCC diagnoses were confirmed using immunohistochemistry.

Results. Three cases of MCC were detected among 4200 individuals who underwent renal transplantation from 1967 to 2005 [expected number 0.05, standardized incidence ratio (SIR) 66, 95% CI 14–194, P <0.001]. The latency period between the transplant and detection of MCC ranged from 6 to 19 years. In all three cases, the cause of