Title: Cancer mortality in kidney transplant recipients: an Australian and New Zealand population-based cohort study, 1980-2013

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Abbreviations: Australian and New Zealand Dialysis and Transplantation Registry (ANZDATA); Australian Institute of Health and Welfare (AIHW); Human Research Ethics Committee (HREC); International Classification of Diseases, Ninth Revision (ICD-9); Inter-quartile Range (IQR); International Statistical Classification of Diseases, 10th revision, Australian Modification (ICD10AM); Mortality Data Collection (MORT); National Death Index (NDI); Standardised Mortality Ratio (SMR; United States of America (USA); Person-years of follow-up (pys);

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Novelty and Impact:

This bi-national data-linkage population study of 17,628 kidney transplant recipients followed over 175,000 person-years demonstrated cancer mortality has remained 3-times that of the general population since 1980. Relative cancer mortality risk varied by site, age, country, sex, and was highest for cancers associated with immunosuppression therapy including non-melanoma skin cancers and lymphoma. It is not clear whether excess mortality is due to differences at diagnosis or in access and effectiveness of cancer treatment in this population.

Abstract:

Cancer burden is increasing in kidney transplant recipients, but differences in mortality compared to the general population remain unclear. We sought to compare cancer mortality in paediatric and adult kidney transplant recipients with the general population and describe any differences, by site, age and sex, country, and over time. We included kidney transplant recipients from the Australian and New Zealand Dialysis and Transplantation Registry, 1980-2013. Date of death and underlying cause of death were ascertained by data-linkage and classified using ICD10AM codes. Indirect standardization was used to estimate standardized mortality ratios (SMR). There were 5,284 deaths in 17,628 kidney transplant recipients over 175,084 person-years of observation, including 1,061 (20%) cancer deaths. Relative cancer mortality was higher than the general population for all-site (SMR 2.9, 95%CI 2.7-3.1) cancer and highest for non-melanoma skin cancer (SMR 50.9, 95%CI 43.5-59.6) and lymphoma (SMR 42.2, 95%CI 35.3-50.5). Relative cancer mortality decreased with increasing age in men ($p<0.001$) and women ($p=0.001$) but never reached parity with the general population. Relative mortality did not change with age for skin and lip, or colorectal cancers (p-value >0.1). Only relative colorectal cancer mortality increased over time ($p=0.002$). Our study shows cancer mortality in kidney transplant recipients was higher than expected in the general population. The magnitude of excess mortality varied by cancer site, age and sex. Further evidence is needed to identify whether this variation is due to differences at diagnosis or access and effectiveness of cancer treatments in this population.

Introduction:

The increase in cancer incidence for most sites in transplant recipients has been well described. Most cancers are viral-associated including Kaposi's sarcoma and non-Hodgkin's Lymphoma or, known to be increased when immune surveillance is decreased including non-melanoma skin cancers [1, 2]. This is attributed to long-term duration of immunosuppression therapy necessary to maintain a functioning transplant [3]. Age-standardised cancer mortality is decreasing in the Australian general population [4]. Kidney transplant recipients have 2-3 times the cancer mortality risk of the general population [5]. However, how cancer mortality has changed over time, or how mortality differs by age, sex or country of residence is unclear.

Cancer is now the leading cause of death in kidney transplant recipients in Australia and New Zealand, contributing to 30% of all deaths in 2017 [6]. Improvements in cardiovascular disease prevention and treatment and immunosuppression therapy have reduced cardiovascular mortality and increased recipient survival with a functioning transplant [7]. Over time, recipients have thus experienced a longer duration of immunosuppression, placing them at greater risk of cancer. Furthermore, in the past 30 years there has been a trend towards transplanting older recipients with higher chronic disease burden [8]. As the chronic-disease burden in kidney transplant recipients is increasing, it is important to understand whether cancer drives mortality and, whether improvements in cancer mortality in the general population are mirrored in the transplant population.

Previous work exploring cancer mortality in solid organ transplant recipients has been limited by data sources and population coverage, for transplant recipients or comparators, and differences in approach to assigning cause of death in transplant recipients and the general population. Estimates from the USA and Canada have described contradictory results; risk of death was not increased in USA transplant recipients but was 3-times higher than the general population in Canada [5, 9]. Relying solely on unverified transplant registry information, without death register information, mortality risk was 2.7 times higher than the general population in Australia [10]. Verification of cause of death using data-linkage to death registry data would provide a more reliable estimate of cancer mortality in transplant recipients and may highlight different trends.

We sought to describe cancer mortality in kidney transplant recipients compared to the general population using bi-national linked data.

Materials and Methods:

Study cohort: We conducted a population-based cohort study of kidney transplant recipients using the Australian and New Zealand Dialysis and Transplantation Registry (ANZDATA). ANZDATA is a bi-national registry in operation since the inception of end-stage kidney disease treatment in Australia and New Zealand, recording demographic, clinical and outcome data for all those in country receiving treatment [11].

To determine fact and cause of death we linked ANZDATA with national death registers in Australia and New Zealand. In both countries' fact and cause of death reporting is mandatory. Australian recipients were linked using probabilistic linkage with the National Death Index (NDI) at the Australian Institute of Health and Welfare (AIHW), based on personal identifiers including first name, surname, gender, date of birth and date of death[12, 13]. New Zealand recipients were linked using deterministic linkage with the Mortality Data Collection (MORT) at the New Zealand Ministry of Health, based on their National Health Index number. Using the latest available data, we included Australian transplant recipients 1980-2013, and New Zealand kidney transplant recipients 1988-2012.

Cause-specific summary level death rates for the general population by age, sex and calendar year were provided by the AIHW for the Australian general population, and by the New Zealand Ministry of Health for the New Zealand general population. Ethics approval for the study was given by The University of Sydney (HREC 2014/917).

Outcome definitions: Cause of death was the underlying cause of death from the respective national death registers, classified using the International Classification of Diseases and Health Related Problems, Tenth Revision, Australian Modification (ICD-10-AM) diagnostic codes [14]. The ICD-10-AM is a derived version of the World Health Organisation ICD-10 developed by the National Centre for Classification in Health to ensure classification is current and appropriate for Australian clinical practice [15]. It includes Australian extensions of the WHO codes in ICD-10 and some specific Australian disease codes [16]. There are no major differences between the classifications of neoplasms (Chapter C) or possible malignant blood disorders (D45-47). Where the cause of death was recorded using the International Classification of Diseases, Ninth Revision (ICD-9) codes, in records prior to 1995 in Australia and prior to 2000 in New Zealand,

they were converted to ICD-10-AM using the ICD-9 to ICD-10-AM conversion map provided by the New Zealand Ministry of Health (New Zealand Ministry of Health, 2000). Cancer deaths were grouped as all-site cancers (ICD-10-AM C00–C97, D45, D46, D47.1 & D47.3–D47.5) as per the classification of all cancers combined by the AIHW (ref 4) for direct comparison of mortality trends over time. Malignant transplant related cancers included malignant cancers except non-melanoma skin and kidney cancers (C00-C97 excluding C44 & C64), which have been clearly linked with transplantation and may be subject to reporting bias compared to the general population. Site-specific cancers were classified based on body system, organ or cancer type (Table 1). Deaths known in ANZDATA that were not captured by national linkages were censored at the date of death given by ANZDATA. Such a situation may arise where an individual die overseas. Less than 1% of participants were excluded where date of death preceded date of transplant.

Statistical Analyses: We observed kidney recipients from the date of first transplant until date of death or 31st December 2013 for Australian patients and 31st December 2012 for New Zealand patients. There was no censoring at graft failure and return to dialysis and removal of immunosuppression. Demographic and clinical characteristics at the time of first transplant were summarised for Australian and New Zealand recipients using absolute counts and proportions. We tested for differences using the Chi-squared test for proportions for categorical variables and the Wilcoxon rank-sum test for continuous variables. To determine absolute risk estimates of mortality, the cumulative incidence function for cancer death was estimated for each country, treating non-cancer death as a competing risk [17].

To compare cancer mortality in kidney transplant population with the general population, we estimated crude rates per 100,000 person-years of follow-up (pys) for all-site and site-specific cancers. We estimated standardised mortality ratios (SMR) for cancer deaths using indirect standardisation, by age sex, calendar year and country. We tested for differences between countries and sex and, conducted linear trend for age using chi-squared tests. To assess changes over time, we used rolling calendar year averages [18].

Results:

There were 17,628 transplant recipients included in the final analysis (**Figure 1**), 88% Australian and 12% New Zealand, with a total follow-up of 175,084 person years and a median follow-up time of 8.3 years (IQR 3.6-13.7). Of these, 5,284 recipients died (4,734 Australian and

550 New Zealand). Of all deaths, 29 (<1%) did not have an ICD10 coded cause of death, 21 of which were Australian transplant recipients who died the year of linkage and were not yet coded.

Baseline characteristics for Australian and New Zealand recipients are described in **Table 1**. At the time of first transplant, Australian recipients were older and had spent more time on dialysis compared to New Zealand recipients. The proportion of males to females was similar in both countries. New Zealand had a higher proportion of recipients with indigenous background. New Zealand recipients were also more likely to have a history of smoking, and be transplanted after the year 2000.

Cancer mortality

There were 5,284 deaths, of which 1,061 (20%) were due to cancer. Cancer was the second leading cause of death in our cohort, following cardiovascular disease. As for non-cancer deaths, the cumulative incidence of cancer death increased over time post-transplant, but at a lower rate (**Figure 2**). Risk of cancer death was not limited to long-surviving recipients but increased steadily over time without an apparent plateau; 1% at 2 years post-transplant, 2% at 5 years, 5% at 10 years, 10% at 20 years, and 14% at 30 years.

The most common cancer deaths in both nations combined were those of the skin and lip (21%), digestive system (18%) and blood and lymphatic system (16%) (**Supplementary Table 1**). There were 124 (12%) cancer deaths of unspecified or multiple primary sites (118 in Australia and 6 in New Zealand).

The crude cancer mortality rate was 606 (95%CI 570.6–643.6) per 100,000 pys and increased with age (p-value <0.05). Cancer mortality was higher in males (662; 95%CI 615.0–713.6 per 100,000 pys) than females (522; 95%CI 471.1–578.1 per 100,000 pys).

Cancer mortality risk compared to the general population:

Relative cancer mortality in kidney transplant recipients was significantly elevated for several, but not the most frequent (i.e., breast and prostate) cancer sites compared to the age, sex and year standardised general population in both countries. Risk of all-site cancer death was 3 times (SMR 2.9, 95%CI 2.7-3.1) higher in recipients than the general population with no difference between males (SMR 2.9, 95%CI 2.7–3.1) and females (SMR 3.0, 95%CI 2.7–3.3; p=0.6). Malignant non-transplant related cancers (malignant cancers excluding non-melanoma skin and kidney) had 2.3 times the risk of death compared to the general population. Cancer

mortality risk was increased in 15 of 18 site-specific cancers identified compared to the general population (**Figure 3**). Non-melanoma skin cancer (SMR 50.9, 95%CI 43.5-59.6), lymphoma (SMR 42.2, 95%CI 35.3-50.5) and oral and pharynx cancer (SMR 33.0; 95%CI 21.75-50.17) carried the highest relative risk of cancer death. There was no excess risk of death from breast (SMR 1.1; 95%CI 0.8-1.6), prostate (SMR 1.6; 95%CI 0.7-1.6) cancer or multiple myeloma (SMR 1.6; 95%CI 0.8-3.2).

All-site relative cancer mortality risk decreased as age increased in male recipients (p-value ≤ 0.001) but remained elevated compared to general population levels (**Figure 4**); all-site relative cancer mortality risk was increased 9-fold for ≤35-year-olds, 3-fold in 45-54-year-olds and 2-fold in ≥65-year-olds. For female recipients, relative mortality risk for all-site cancer was 8-fold higher than the general population in ≤35-year-olds but remained steady from the age of 35 (SMR 2.3 – 3.0) (**Supplementary Table 2**). Relative mortality risk decreased with increasing age for both female and male recipients for lymphoma and for kidney and lung cancer in males (p-value < 0.05). Conversely, relative mortality risk did not change with age for colorectal and skin and lip cancers (p-value > 0.1). Females also had unchanging relative risk of cancer death across all age groups for lung and kidney cancers (p-value > 0.1). Non-melanoma skin cancer had the highest cancer mortality risk in females (SMR 74; 95%CI 51.0-102.9) and males (SMR 47; 95%CI 38.8-56.0), followed by oral and pharynx cancer in females (SMR 71; 95%CI 30.8-140.5) and lymphoma in males (SMR 46; 95%CI 36.7-56.2) (**Supplementary Table 3**).

Relative cancer mortality risk did not change between 1980 and 2013 for all-site, kidney, lung, skin and lip cancers, or lymphoma (p-value > 0.1) (**Figure 5**). There was evidence of a linear temporal increase in SMR for colorectal cancer (X^2_{1df}=10.0, p=0.002). Colorectal cancer mortality was 3 times (SMR 2.8, 95%CI 0.8-7.1) higher than the general population between 1980-1990 and remained 5-6 times (SMR 6.1, 95%CI 4.4-8.2) higher since 2000.

Risk of all-site cancer death did not differ by country (Australia SMR 2.9; 95%CI 2.7-3.0 and New Zealand SMR 3.2; 95%CI 2.8-3.9; p=0.1). Cancer mortality risk for cancers of the liver and brain, eye and central nervous system were significantly increased in Australian recipients (SMR 2.5, 95%CI 1.7-3.7 and SMR 4.9, 95%CI 2.9-7.9) but not in New Zealand (**Supplementary Figure 1**).

Discussion:

We found an increased relative mortality risk for most cancers in kidney transplant recipients compared to the general population, which has not changed over 30 years. The relative risk of death varied by cancer site, sex, age and country. Site-specific cancer relative mortality risk followed the pattern of site-specific cancer incidence in kidney transplant recipients [2]. Cancers with the highest relative mortality risk were viral-associated including, lymphoma (associated with Epstein Barr Virus infection) and, cancers thought to be associated with impaired immune surveillance such as non-melanoma and melanoma skin cancers. Conversely, the relative risk of death for cancers with high mortality burden in the general population including, breast cancer in females and prostate in males were not increased in our cohort. The novel contribution of our study design is threefold; through data linkage we were able to use verified ICD-10AM causes of death, capture non-melanoma skin cancer deaths and, to access New Zealand data.

Our study builds upon prior estimates of cancer mortality in transplant recipients with long-term follow-up, which found all-site cancer and malignant non-transplant related cancer mortality risk was similarly increased over the general population (SMR 2-3) and highest in the young [5, 10]. However, we found this is not true for all cancer types. Our results show relative cancer mortality risk did not change with age for cancers of the skin and lip and, colorectal cancer. The higher risk of all-site cancer death in younger recipients can be explained by the relatively fewer cancer deaths in the young in the general population. Decreased relative mortality risk for all-site cancer in older recipients has been attributed to increased competing causes of death in the older transplant population [5]. One explanation for this could be the relatively low mortality rate of colorectal cancers and non-melanoma skin cancers, including squamous cell carcinomas, in the general population. However, absolute risk of death is higher in people over 65 in the general population for both colorectal, melanoma and non-melanoma skin cancers [4]. Our results show that mortality increases proportionally over the general population rates for these cancers, across all age groups. Generally, solid organ cancers after transplantation are more aggressive. It may be that colorectal and skin and lip cancers outcompete other comorbidities, driving death in these age groups. These results reinforce the need to develop site-specific cancer management strategies post-transplant, based on risk-profile of specific age groups.

In our cohort non-melanoma skin cancer had the highest excess mortality compared to the general population. In the general population death from non-melanoma skin cancer death is uncommon [4]. Australian kidney transplant recipients have the highest incidence of skin cancers globally, including non-melanoma skin cancers [19]. A cross-sectional Australian study found that 21% of kidney transplant recipients had confirmed non-melanoma skin cancer within a 3 months screening period [20]. The increased relative risk of non-melanoma skin cancer death in kidney transplant recipients could be indicative of increased incidence and differences in tumour development and aggressiveness, and suggestive of ineffective cancer treatment. There are few studies investigating outcomes of recipients with NMSC. However, post-transplant cutaneous melanomas are more invasive, have a greater tendency to metastasise and carry higher risk of death in recipients compared to non-transplant melanoma cancer patients [21]. Poorer survival has been attributed to inhibition of the immune response to melanoma due to immunosuppression and may suggest treatment algorithms developed for the general population may not be effective in transplant recipients. Transplant recipients in the US with melanomas are also less likely to undertake surgery, radiotherapy or chemotherapy compared to the general population [22]. Whether this is the case for Australian and New Zealand given differences in healthcare systems, needs further investigation.

Our results show excess cancer mortality in Australian and New Zealand kidney transplant recipients has not changed in the past 30 years for most cancer types. This indicates that the decrease in age-standardised cancer mortality seen in the general population is mirrored in the kidney transplant population. However, it also demonstrates that the relative risk of cancer mortality remains higher than the general population. This may be a result of increased cancer incidence in kidney transplant recipients, which is associated with type, intensity and duration of immunosuppressive therapy [3]. Consecutive reports from the ANZDATA registry, which include recipients transplanted between 1980-2013 suggest that transplant immunosuppression type given to kidney transplant recipients has remained largely unchanged in the past 30 years[23]. Most recipients in Australia and New Zealand are on Calcineurin Inhibitors (Tacrolimus and Cyclosporin). Less than 5% of transplant recipients have received mTOR inhibitor between 2010-2017. Alternatives to current immunosuppression therapies that may better balance risk of cancer and infection with loss of the transplant and mortality are still being explored with varying results. For example, studies have demonstrated up to a 40% reduction in risk of cancer development with the use of

mammalian target of rapamycin, sirolimus, compared to CNI, however, this was at an increased risk of increased all-cause mortality [24].

Increased cancer mortality in kidney transplant recipients may be also indicative of impaired effectiveness of cancer therapies in immune suppressed individuals. There is little evidence demonstrating the benefit and harms of cancer therapies in kidney transplant recipients. Many chemotherapies have significant side-effects such as neutropenia which may lead to serious infections in already immune suppressed recipients and nephrotoxicity which may lead to damage or loss of the transplant [25]. There is some evidence that chemotherapies can be used safely in transplant recipients when balanced with a relative reduction in immunosuppression [26]. However, this is yet to be validated in larger studies.

There were some limitations to the current study. We did not quantify site-specific SMR where numbers were too low for an accurate estimate, such as in younger age groups. Instead, we focused on age groups where the cancer burden was the greatest in the general population. As we did not link to existing cancer registries we were unable to test for differences in cancer mortality between recipients with and without a history of cancer prior to transplantation. There was a large proportion of cancer deaths with unknown primary site in Australia, which may reflect patients with advanced stage malignancy at diagnosis, who were not fit for curative therapy, and were spared from unnecessary testing. In the general population cancer mortality due to unknown primary site diagnosis has decreased since 1982 [4]. Such loss of information can underestimate site-specific cancer mortality burden in kidney transplant recipients and may negatively impact the assessment of site-specific prevention and treatment strategies in the future.

The major strengths of this study were minimal loss to follow-up due to data linkage with national mortality registers. Data-linkage provided a large study cohort, with verified cause of death and longer follow-up compared to other cohort studies, from which we were able to confidently stratify site-specific cancers by age, sex, country and calendar year. We were also able to capture non-melanoma skin cancers. The disease burden of non-melanoma skin cancer in Australia and New Zealand is not well documented. Incident non-melanoma skin cancers are non-notifiable, making population-based estimates of cancer incidence difficult. Previous Australian studies attribute the highest excess mortality to viral related cancers including post-transplant lymphoproliferative, but were unable to capture non-melanoma skin cancer death

[10]. Here we provide population-based estimates of the non-melanoma skin cancer mortality burden in kidney transplant recipients in Australia and New Zealand based on population data.

Our findings show that relative mortality risk has remained increased above general population levels for the past 30 years. This increased risk highlights the need for better evidence for post-transplant cancer diagnosis, management and treatment in kidney transplant recipients and, reinforce the need for cancer prevention and early diagnosis by patients and clinicians. Furthermore, we found there is a difference in the magnitude of relative cancer mortality risk based on cancer site, and that not all cancer types follow the same trend in mortality over age and sex as all-site cancer. These differences in mortality based on cancer type highlight the need for targeted site-specific cancer prevention and treatment strategies. Our results could be used to identify recipients at higher risk of cancer death, assist in discussing mortality risk with recipients and inform future studies in targeted cancer treatments in this population.

In conclusion, we found the relative cancer mortality risk in kidney transplant recipients has not changed, despite improvements in cancer diagnosis and treatments decreasing cancer mortality in the general population. Further investigation into what is driving differences in site-specific cancer mortality and better methods of prevention and treatment is warranted.

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References:

1. Grulich, AE, van Leeuwen, MT, Falster, MO, Vajdic, CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet.* 2007;370: 59-67.

2. Vajdic, CM, McDonald, SP, McCredie, MR, van Leeuwen, MT, Stewart, JH, Law, M, Chapman, JR, Webster, AC, Kaldor, JM, Grulich, AE. Cancer incidence before and after kidney transplantation. *JAMA.* 2006;296: 2823-31.

3. Gallagher, MP, Kelly, PJ, Jardine, M, Perkovic, V, Cass, A, Craig, JC, Eris, J, Webster, AC. Long-term cancer risk of immunosuppressive regimens after kidney transplantation. *J Am Soc Nephrol.* 2010;21: 852-8.

4. Australian Institute of Health and Welfare, Cancer in Australia 2017. A.I.H.W, 2017.

5. Acuna, SA, Fernandes, KA, Daly, C, Hicks, LK, Sutradhar, R, Kim, SJ, Baxter, NN. Cancer Mortality Among Recipients of Solid-Organ Transplantation in Ontario, Canada. *The Journal of the American Medical Association Oncology.* 2016;2: 463-9.

6. ANZDATA Registry, Chapter 3: Mortality in End Stage Kidney Disease. Australia and New Zealand Dialysis and Transplant Registry,, 2018.

7. Pilmore, H, Dent, H, Chang, S, McDonald, SP, Chadban, SJ. Reduction in cardiovascular death after kidney transplantation. *Transplantation.* 2010;89: 851-7.

8. Lam, NNMDM, Kim, SJMDP, Knoll, GAMDM, McArthur, EM, Lentine, KLMDP, Naylor, KLMES, Li, AHB, Shariff, SZP, Ribic, CMMDM, Garg, AXMDP. The Risk of Cardiovascular Disease Is Not Increasing Over Time Despite Aging and Higher Comorbidity Burden of Kidney Transplant Recipients. *Transplantation.* 2017;101: 588-96.

9. Kiberd, BA, Rose, C, Gill, JS. Cancer mortality in kidney transplantation. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons.* 2009;9: 1868-75.

10. Au, EH, Chapman, JR, Craig, JC, Lim, WH, Teixeira-Pinto, A, Ullah, S, McDonald, S, Wong, G. Overall and Site-Specific Cancer Mortality in Patients on Dialysis and after Kidney Transplant. *J Am Soc Nephrol.* 2019: ASN.2018090906.

11. Sypek, MP, Dansie, KB, Clayton, P, Webster, AC, McDonald, S. Comparison of cause of death between anzdata and the australian national death index. *Nephrology (Carlton).* 2018;[in press doi: 10.1111/nep.13250].

12. Boyd, JH, Randall, SM, Ferrante, AM. Application of Privacy-Preserving Techniques in Operational Record Linkage Centres. In: Gkoulalas-Divanis A, Loukides G. *Medical Data Privacy Handbook*ed. Cham: Springer International Publishing, 2015: 267-87.

13. Lawrence, G, Dinh, I, Taylor, L. The Centre for Health Record Linkage: A New Resource for Health Services Research and Evaluation. *Health Information Management Journal.* 2008;37: 60-2.

14. Australian Consortium for Classification, D. *The International Statistical Classification of Diseases and Related Health Problems, tenth revision, Australian modification (ICD-10-AM/ACHI/ACS)*, Ninth ed. Darlinghurst, NSW: Independent Hospital Pricing Authority, 2015.

15. Australian Consortium for Classification, D. ICD-10-AM/ACHI/ACS, vol. 2019, 2019.

16. Roberts, RF, Innes, KC, Walker, SM. Introducing ICD-10-AM in Australian hospitals. *The Medical journal of Australia.* 1998;169 Suppl: S32.

17. Gooley, TA, Leisenring, W, Crowley, J, Storer, BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med.* 1999;18: 695-706.

18. Farewell, VT. Statistical Methods for Individual-Level Data in Cohort Mortality Studies of Rheumatic Diseases AU - Tom, Brian D. M. *Communications in Statistics - Theory and Methods.* 2009;38: 3472-87.

19. Carroll, RP, Ramsay, HM, Fryer, AA, Hawley, CM, Nicol, DL, Harden, PN. Incidence and prediction of nonmelanoma skin cancer post-renal transplantation: a prospective study in Queensland, Australia. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2003;41: 676-83.

20. Iannacone, MR, Sinnya, S, Pandeya, N, Isbel, N, Campbell, S, Fawcett, J, Soyer, PH, Ferguson, L, Davis, M, Whiteman, DC, Green, AC, Campbell, S, Chambers, D, Davis, M, Fawcett, J, Ferguson, L, Grant, M, Green, A, Hawley, C, Hopkins, P, Isbel, N, Iannacone, M, Lawton, T, Leary, D, Miura, K, Olsen, T, Pandeya, N, Ong, N, Sahebian, A, Sinnya, S, Soyer, HP, Tan, JM, Way, M, Whiteman, D. Prevalence of Skin Cancer and Related Skin Tumors in High-Risk Kidney and Liver Transplant Recipients in Queensland, Australia. *J Invest Dermatol.* 2016;136: 1382-6.

21. Vajdic, CM, Chong, AH, Kelly, PJ, Meagher, NS, Van Leeuwen, MT, Grulich, AE, Webster, AC. Survival After Cutaneous Melanoma in Kidney Transplant Recipients: A Population-Based Matched Cohort Study. *Am J Transplant.* 2014;14: 1368-75.

22. D'Arcy, ME, Coghill, AE, Lynch, CF, Koch, LA, Li, J, Pawlish, KS, Morris, CR, Rao, C, Engels, EA. Survival after a cancer diagnosis among solid organ transplant recipients in the United States. *Cancer.* 2019.

23. Australia and New Zealand Dialysis and Transplant Registry, Chapter 7: Transplantation, 2018.

24. Knoll, GA, Kokolo, MB, Mallick, R, Beck, A, Buenaventura, CD, Ducharme, R, Barsoum, R, Bernasconi, C, Blydt-Hansen, TD, Ekberg, H, Felipe, CR, Firth, J, Gallon, L, Gelens, M, Glotz, D, Gossmann, J, Guba, M, Morsy, AA, Salgo, R, Scheuermann, EH, Tedesco-Silva, H, Vitko, S, Watson, C, Fergusson, DA. Effect of sirolimus on malignancy and survival after kidney transplantation: systematic review and meta-analysis of individual patient data. *BMJ.* 2014;349: g6679.

25. Krisl, JC, Doan, VP. Chemotherapy and Transplantation: The Role of Immunosuppression in Malignancy and a Review of Antineoplastic Agents in Solid Organ Transplant Recipients. *Am J Transplant.* 2017;17: 1974-91.

26. Taylor, AL, Bowles, KM, Callaghan, CJ, Wimperis, JZ, Grant, JW, Marcus, RE, Bradley, JA. Anthracycline-based chemotherapy as first-line treatment in adults with malignant posttransplant lymphoproliferative disorder after solid organ transplantation. *Transplantation.* 2006;82: 375-81.

Table 1. Demographic and clinical characteristics of Australian and New Zealand kidney recipients at time of first transplant

Characteristic	Australia N (%)	New Zealand N (%)	Total N	P-value
Recipeints	15476	2152	17628	
Person years follow-up				
Age (median, IQR)	46 (33-56)	44 (31-55)	45 (33-56)	0.06
Months on dialysis prior to 1st transplant (median, IQR)	19 (8-39)	18 (7-38)	19 (7-39)	0.03
Sex				0.5
Female	6083 (39)	831 (39)	6914	
Male	9393 (61)	1321 (61)	10714	
Body Mass Index (kg/m2)				0.2
Underweight (<18.5)	1094 (9)	152 (8)	1246	
Normal (18.5-24.9)	5702 (45)	853 (44)	6555	
Overweight (25.0-29.9)	3832 (30)	630 (32)	4462	
Obese (≥30.0)	2043 (16)	319 (16)	2362	
Not recorded[a]	2805	198	3003	
Ethnic background				<0.001
European	13,184 (85)	1,530 (71)	14714	
Indigenous [b]	522 (3)	288 (13)	1248	
Asian	1501 (9)	322 (15)	1449	
African & Middle Eastern	160 (1)	7 (<1)	167	
Peoples of the Americas	8 (<1)	2 (<1)	10	
Mixed background	11 (<1)	1 (<1)	12	
Missing	90	2	28	
Smoking history				<0.001
Previous or current smoker	5289 (34)	826 (38)	6115	
Never smoked	10187 (66)	1326 (62)	11513	
Year transplanted				<0.001
1985-1990	3258 (21)	121 (6)	3379	
1991-99	3614 (23)	725 (34)	4339	
2000-09	5577 (36)	989 (46)	6566	
2010-13	3027 (20)	317 (15)	3344	
Primary cause of kidney failure				<0.001
Diabetes	1710 (11)	257 (12)	1967	
Hypertension/renal artery disease	623 (4)	120 (6)	743	
GN/IgA nephropathy	6826 (44)	959 (45)	7785	
Polycystic kidney	1910 (12)	286 (13)	2196	
Other	4407 (29)	530 (25)	4937	
Cerebrovascular disease	414 (3)	66 (3)	480	0.3
Diabetes	2187 (14)	291 (14)	2478	0.4
Coronary artery disease	1310 (9)	164 (8)	1474	0.2
Peripheral vascular disease	762 (5)	103 (5)	865	0.8

a. Height was not routinely recorded in ANZDATA until after 1995. Of the 3003 records with missing BMI, 810 (27%) were missing weight and 2,185 (73%) were missing height.
b. Indigenous includes Australian Aboriginal and Torres Strait Islanders in Australia and Maori in New Zealand.

Figure Legends:

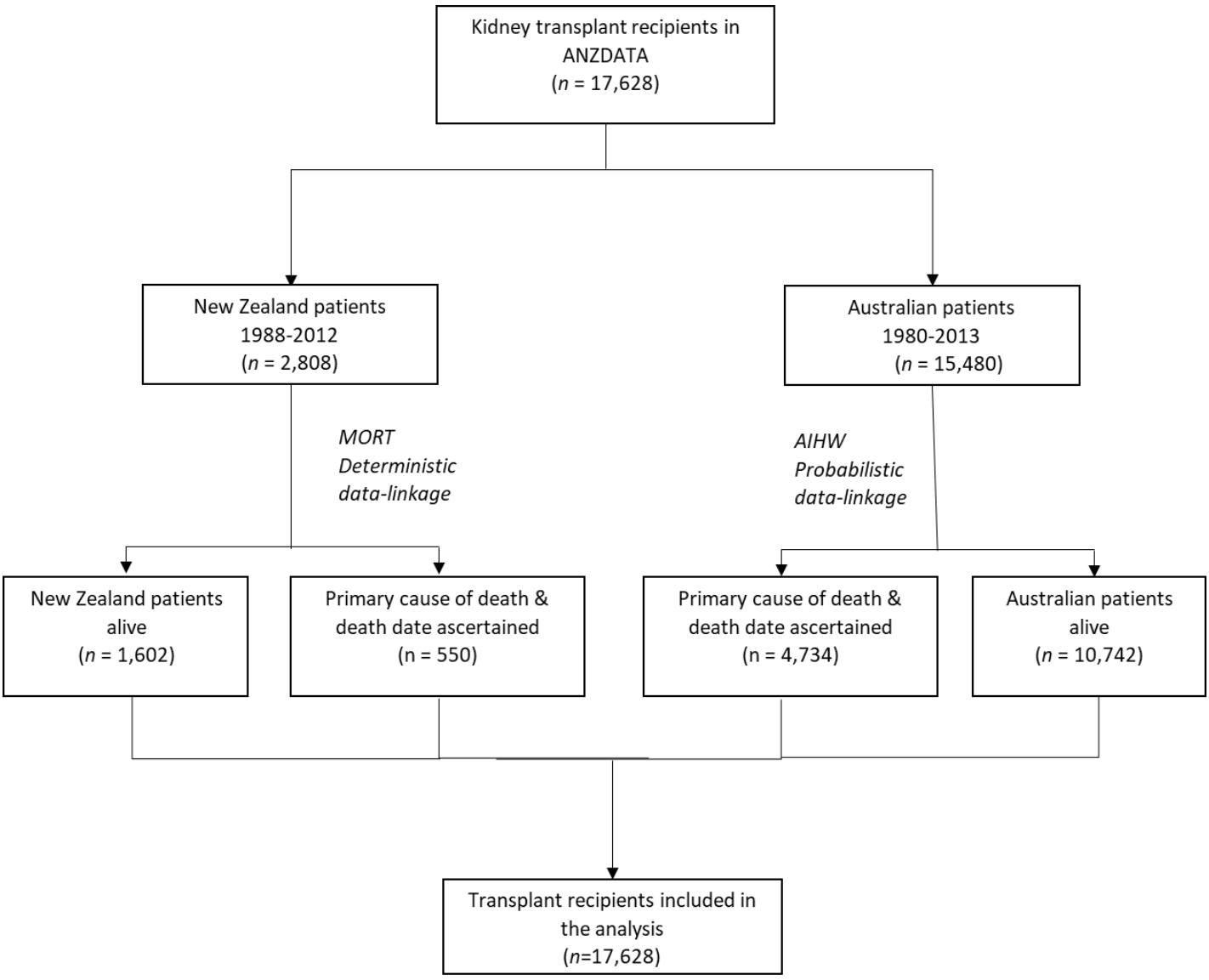


Figure 1. Data-linkage of kidney transplant recipients identified in the Australian and New Zealand Dialysis and Transplant Registry (ANZDATA Registry) with national death databases, the New Zealand Mortality Data Collection (MORT) and the Australian Institute of Health and Welfare (AIHW) National Deaths Index (NDI).

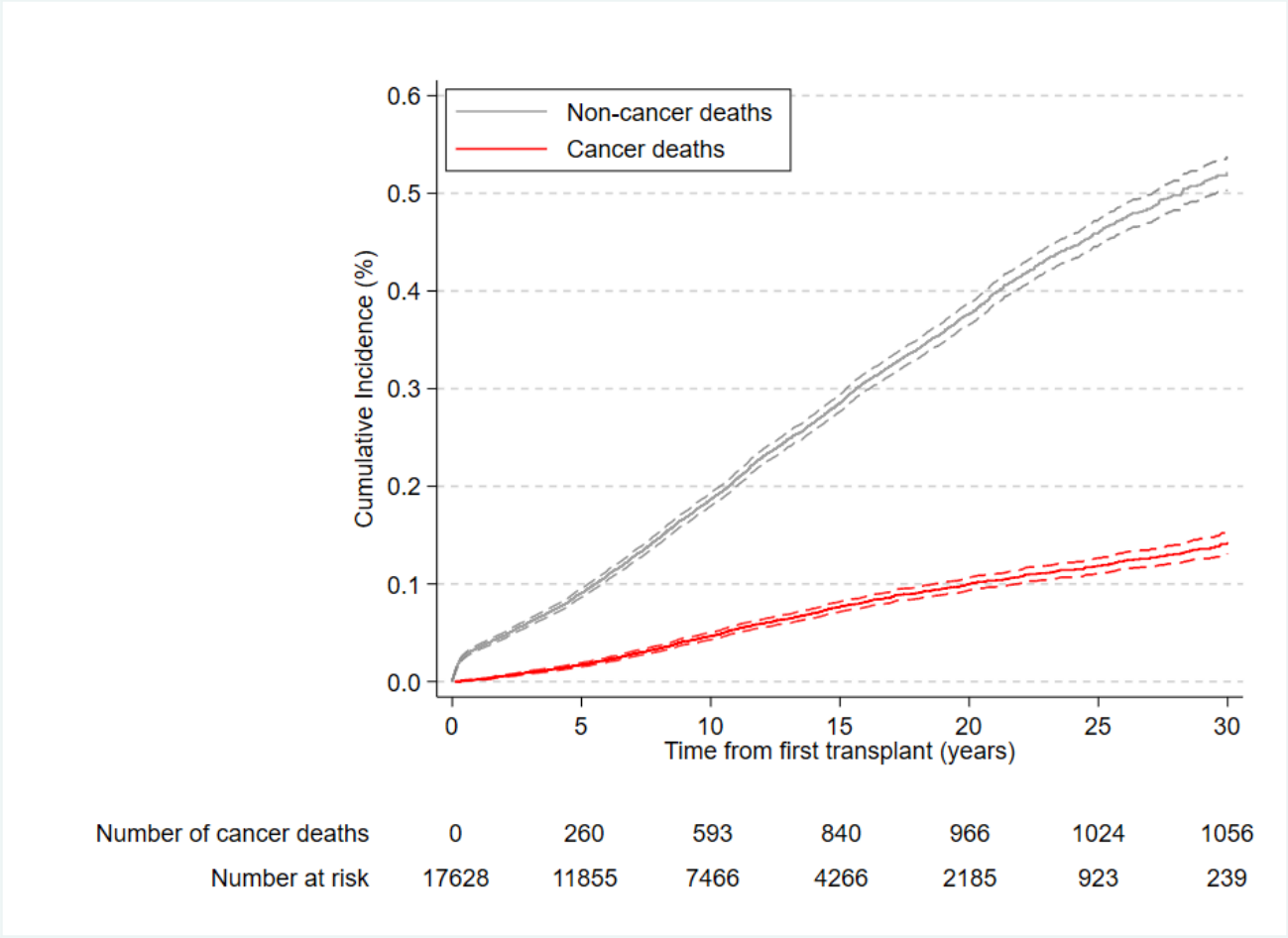


Figure 2: Cumulative incidence of cancer and non-cancer deaths in Australian and New Zealand kidney transplant recipients by number of years from first transplant. 95% confidence intervals shown in dotted lines.

Cancer Site	ICD-10-AM	Deaths (N)	Expected deaths (N)	SMR (95%CI)
Non-melanoma skin	C44	154	3.0	51 (43.5-59.6)
Lymphoma	C81-C86	121	4.0	31 (25.6-36.5)
Oral and pharynx	C01-C14	22	1.3	17 (11.0-25.3)
Unspecified	C76, C80, C97	124	8.6	14 (12.1-17.3)
Kidney	C64, C79	74	6.9	11 (8.6-13.6)
Leukaemia	C91-C95	28	3.3	8.4 (5.8-12.1)
Soft tissue	C45-C49	15	2.3	6.5 (3.9-10.8)
Melanoma	C43	69	13.3	5.2 (4.1-6.6)
Colorectal	C18-20	72	18.8	3.8 (3.0-4.8)
Brain, eye & CNS	C69-C72	17	4.8	3.5 (2.2-5.7)
Endocrine	C73-C75	2	0.6	3.4 (0.8-13.4)
Lung	C33-C34	122	45.2	2.7 (2.3-3.2)
Cervix	C53	6	2.3	2.6 (1.2-5.7)
Anus	C21	7	2.7	2.5 (1.2-5.3)
Liver	C22	26	11.1	2.3 (1.6-3.4)
Multiple myeloma	C90	8	5.5	1.5 (0.7-2.9)
Breast	C50	26	23.4	1.1 (0.8-1.6)
Prostate	C61	19	18.6	1.0 (0.7-1.6)
All-site	C00-C97, D45, D46, D47.1, D47.3-D47.5	1061	365.8	2.9 (2.7-3.1)
Malignant (excl. NMSC & kidney)	C00-C97 (excl. C44 & C64)	822	352.0	2.3 (2.2-2.5)

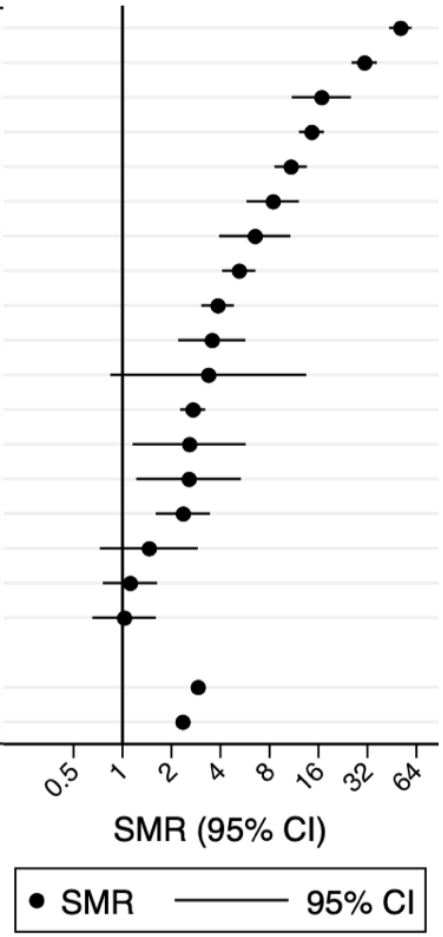


Figure 3: Site-specific cancer observed deaths vs expected deaths and standardised mortality ratios (SMR) in Australian and New Zealand kidney transplant recipients.

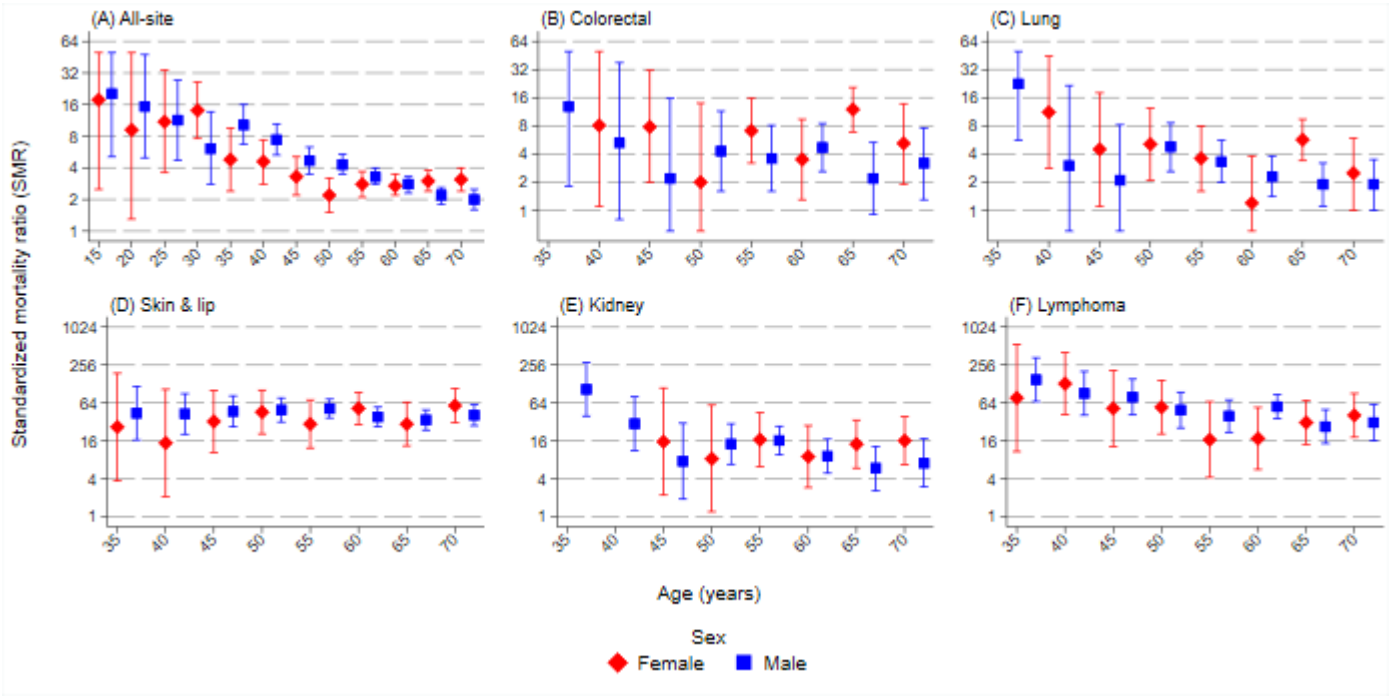


Figure 4: Standardised mortality ratios (SMR) in male and female transplant recipients in Australia and New Zealand combined by 5-year age-groups for (A) all-site, and (B) colorectal, (C) lung, (D) skin and lip, (D) kidney cancers and (E) lymphoma. Upper age limits are shown. Where no cancer deaths were recorded in an age-group for site-specific cancers an SMR point has not been plotted.

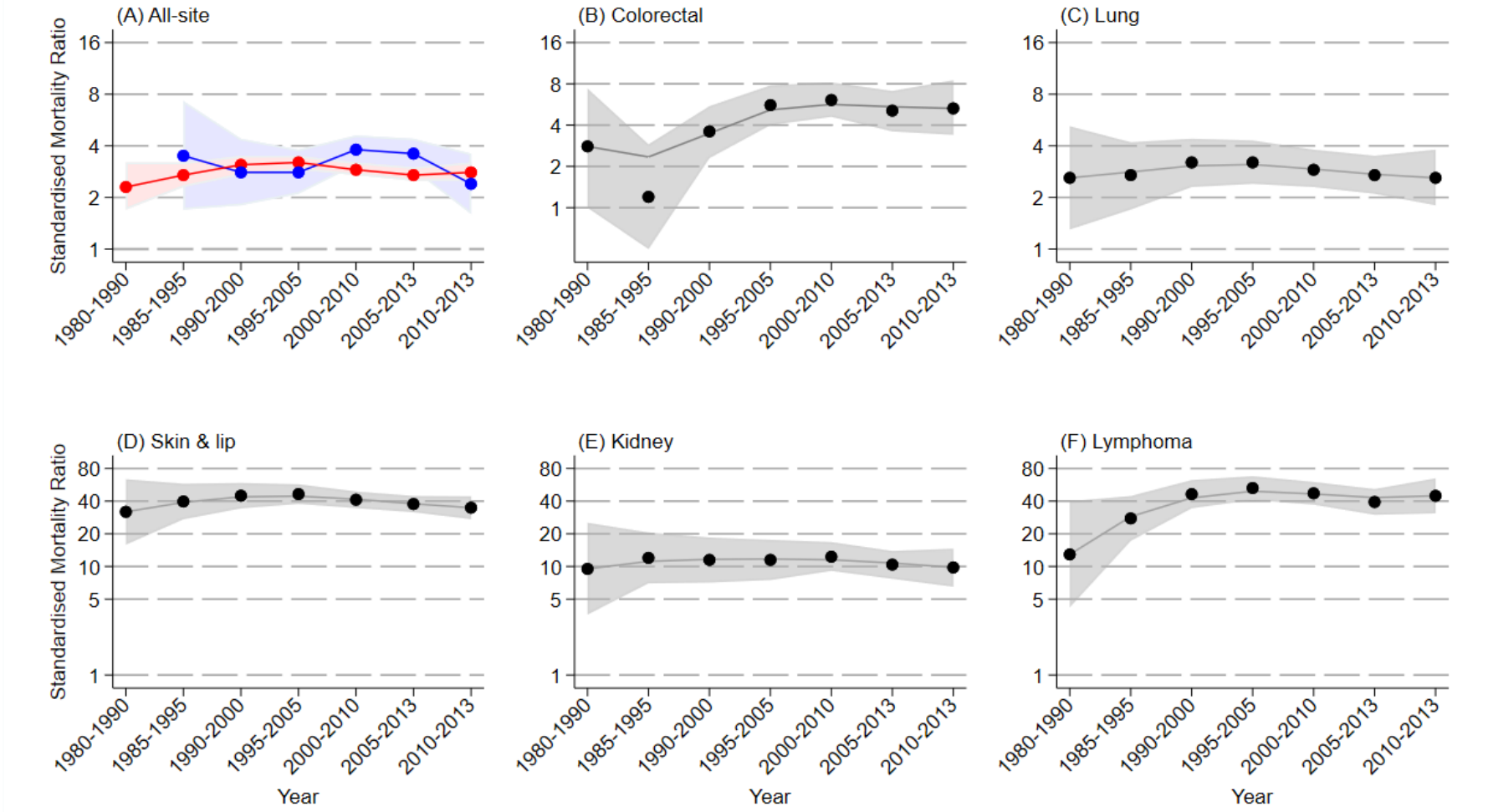


Figure 5:
Rolling average of standardised mortality ratios (SMR) in Australian and New Zealand kidney transplant recipeints for (A) all-site and in recipients of both countries combined for (B) colorectal, (C) lung, (D) skin and lip, (D) kidney cancers and (E) lymphomas by overlapping 10-year periods.

Supplementary Table 1: Cancer death classification, number of deaths and mortality rate for all-site and site-specific cancers in kidney transplant recipients, Australia and New Zealand 1980-2013

Cancer Site	ICD-10-AM	Deaths (N)	Mortality rate per 100,000 pys (95%CI)
Oral and pharynx	C01-C14	22	13 (8-19)
Digestive organs	C15-C26	188	107 (93-124)
Colorectal	C18-20	72	41 (33-52)
Anus	C21	7	4 (2-8)
Liver	C22	26	15 (10-22)
Respiratory & intrathoracic	C30-39, C78	127	73 (61-86)
Lung	C33-C34	122	70 (58-83)
Skin & lip	C00, C43-C44	225	129 (113-146)
Melanoma	C43	69	39 (31-50)
Non-melanoma skin	C44	154	88 (75-103)
Soft tissue	C45-C49	15	9 (5-14)
Mesothelial	C45	9	5 (3-10)
Breast	C50	26	15 (10-22)
Female genital	C51-C58	16	9 (6-15)
Cervix	C53	6	3 (2-8)
Male genital	C60-C63	22	13 (8-19)
Prostate	C61	19	11 (7-17)
Urinary	C64-C68, C79	101	58 (47-70)
Kidney	C64, C79	74	42 (34-53)
Brain, eye & central nervous system	C69-C72	18	10 (7-16)
Endocrine	C73-C75	2	1 (0.3-5)
Blood & lymphatic system	C81-C96, D45, D46, D47.1, D47.3-D47.5	173	99 (85-115)
Lymphoma	C81-C86	121	69 (58-83)
Multiple myeloma	C90	8	5 (2-9)
Leukaemia	C91-C95	28	16 (11-23)
Unspecified	C76, C80, C97	124	71 (59-85)
All-site	C00-C97, D45, D46, D47.1, D47.3-D47.5	1061	606 (571-643)
All malignant (excl. NMSC & kidney)	C00-C97 (excl. C44 & C64)	822	

Supplementary Table 2: Cancer mortality rate and standardised mortality ratio (SMR) by age and sex at time of first transplant

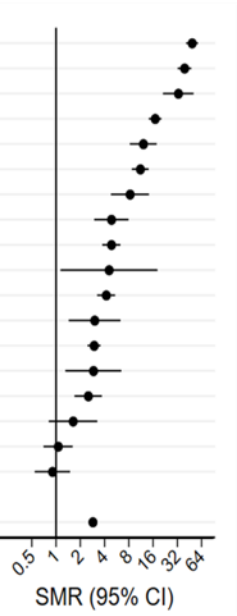
Age group at transplant (Years)	Observed	Expected	Mortality per 100,000 pys (95% CI)	SMR (95% CI)
Female				
≤ 35	55	7.2	213 (163.3-277.0)	7.6 (5.9-10.0)
35-44	44	16.8	285 (211.9-382.6)	2.6 (1.9-3.5)
45-54	86	37.7	553 (447.9-683.6)	2.3 (1.9-2.8)
55-64	142	47.5	1269 (1076-1496)	3.0 (2.5-3.5)
≥ 65	40	14.9	1756 (1288-2394)	2.7 (2.0-3.7)
Male				
≤ 35	93	10.5	242 (197.5-296.5)	8.9 (7.3-10.9)
35-44	109	27.7	459 (380.7-554.2)	3.9 (3.3-4.8)
45-54	219	71.0	917 (802.9-1046)	3.1 (2.7-3.5)
55-64	209	96.6	1356 (1184-1553)	2.2 (1.9-2.5)
≥ 65	66	36.2	2004 (1575-2551)	1.8 (1.4-2.3)

Supplementary Table 3. Number of observed, expected and standardised mortality ratios (SMR) for site-specific cancer deaths by sex

Cancer site	Female			Male		
	Observed (N)	Expected (N)	SMR (95% CI)	Observed (N)	Expected (N)	SMR (95% CI)
All-site	367	124	3.0 (2.7-3.3)	694	242	2.9 (2.7-3.1)
Oral and pharynx	8	0.1	71.0 (30.8-140.5)	14	0.6	25.3 (13.8-42.4)
Digestive organs	91	2.6	34.6 (27.9-42.5)	97	6.3	15.4 (12.5-18.8)
Colorectal	35	5.4	6.5 (4.6-9.1)	37	10.5	3.5 (2.5-4.8)
Anus	5	0.9	5.8 (1.9-13.5)	2	1.9	1.1 (0.1-3.8)
Liver	12	2.3	5.1 (2.7-9.0)	14	8.7	1.6 (0.9-2.7)
Respiratory and intrathoracic	45	2.9	15.7 (11.5-21.0)	82	7.7	10.6 (8.4-13.2)
Lung	42	11.8	3.6 (2.6-4.8)	80	30.8	2.6 (2.1-3.2)
Skin and lip	49	1.3	38.8 (28.7-51.3)	176	4.4	40.2 (34.5-46.6)
Melanoma	15	3.2	4.7 (2.7-7.8)	54	10.1	5.3 (4.0-7.0)
Non-melanoma skin	34	0.5	73.7 (51.0-102.9)	120	2.6	46.8 (38.8-56.0)
Soft tissue	5	0.4	11.5 (3.7-26.8)	10	1.3	7.5 (3.6-13.7)
Mesothelial	1	0.6	1.7 (0.04-9.2)	8	4.4	1.8 (0.8-3.6)
Urinary	33	0.9	36.9 (25.4-51.9)	68	2.8	24.2 (18.8-30.6)
Kidney	20	1.7	11.7 (7.1-18.0)	54	5.1	10.5 (7.9-13.7)
Brain, eye & central nervous system	7	1.1	6.1 (2.4-12.6)	10	2.6	3.8 (1.8-7.1)
Endocrine	1	0.2	4.8 (0.12-27.0)	1	0.3	3.4 (0.1-18.8)
Blood & lymphatic system	44	0.7	62.3 (45.3-83.6)	129	1.5	83.3 (69.5-98.9)
Lymphoma	32	0.9	34.9 (23.9-49.3)	89	1.9	45.7 (36.7-56.2)
Multiple myeloma	2	1.8	1.1 (0.1-4.1)	6	3.8	1.6 (0.6-3.5)
Leukaemia	9	0.7	12.3 (5.6-23.4)	19	1.7	11.4 (6.8-17.7)

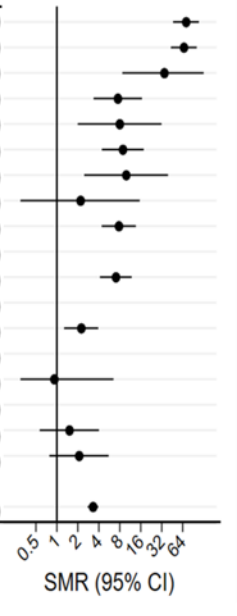
(A) Australia

Cancer Site	ICD10-AM	Observed deaths (N)	Expected deaths (N)	SMR (95% CI)
Non-melanoma skin	C44	133	3	49 (41-58)
Lymphoma	C81-C86	100	3	39 (32-48)
Oral and pharynx	C01-C14	20	1	33 (21-51)
Unspecified	C76, C80, C97	118	7	17 (14-20)
Leukaemia	C91-C95	26	2	12 (8-18)
Kidney	C64, C79	66	6	11 (9-14)
Soft tissue	C45-C49	13	2	8 (5-14)
Brain, eye & CNS	C69-C72	16	3	5 (3-8)
Melanoma	C43	57	12	5 (4-6)
Endocrine	C73-C75	2	0	5 (1-18)
Colorectal	C18-20	58	14	4 (3-5)
Anus	C21	7	2	3 (1-6)
Lung	C33-C34	110	37	3 (2-4)
Cervix	C53	6	2	3 (1-6)
Liver	C22	25	10	3 (2-4)
Multiple myeloma	C90	8	5	2 (1-3)
Breast	C50	22	21	1 (1-2)
Prostate	C61	15	17	1 (1-1)
All-site	C00-C97, D45, D46, D47.1, D47.3-D47.5	937	328	3 (3-3)



(B) New Zealand

Cancer Site	ICD10-AM	Observed deaths (N)	Expected deaths (N)	SMR (95% CI)
Non-melanoma skin	C44	21	0.3	71 (47-109)
Lymphoma	C81-C86	21	0.3	66 (43-102)
Oral and pharynx	C01-C14	2	0.1	35 (9-139)
Unspecified	C76, C80, C97	6	0.8	7 (3-17)
Leukaemia	C91-C95	2	0.3	8 (2-32)
Kidney	C64, C79	8	0.9	9 (4-18)
Soft tissue	C45-C49	2	0.2	10 (2-39)
Brain, eye & CNS	C69-C72	1	0.5	2 (0-15)
Melanoma	C43	12	1.6	8 (4-14)
Endocrine	C73-C75	0	0.1	0 (.-.)
Colorectal	C18-20	14	2.0	7 (4-12)
Anus	C21	0	0.4	0 (.-.)
Lung	C33-C34	12	5.4	2 (1-4)
Cervix	C53	0	0.3	0 (.-.)
Liver	C22	1	1.1	1 (0-7)
Multiple myeloma	C90	0	0.6	0 (.-.)
Breast	C50	4	2.6	2 (1-4)
Prostate	C61	4	1.9	2 (1-6)
All-site	C00-C97, D45, D46, D47.1, D47.3-D47.5	124	37.60	3 (3-4)



Supplementary Figure 1: Site-specific cancer observed deaths vs expected deaths and standardised mortality ratios (SMR) in (A) Australian and (B) New Zealand kidney transplant recipients.