CHAPTER 10

CANCER REPORT

Jeremy Chapman

and

Angela Webster

This report summarises the cancer (excluding non-melanocytic skin cancer) experience of patients treated for end stage renal failure in Australia and New Zealand from 1963 until September 2003.

The first part of the report summarises the relative risk of cancer for patients on dialysis or after at least one kidney transplant, when compared to the general population of Australia. The criteria and methods used for these new analyses are different from those used previously in ANZDATA reports, and have been developed to increase the generalisability of the results and to better reflect observed clinical experience of renal units across Australia and New Zealand.

These analyses are calculated using the method of indirect standardisation by age, gender and calendar year from 1980 – 2003, using national Australian cancer rates supplied by the Australian Institute of Health and Welfare (AIHW). In practical terms this means that the analyses take into account change in risk that may occur through differences in the age and gender distribution between the ESRF population and that of the referent general population, and also differences that may have occurred over time, and so the final calculation is adjusted for these differences. Previous ANZDATA reports analyses have been restricted to comparing cancer risk of ESRF patients to the incidence experienced in the South Australian population at more limited time points.

The number of observed cases of cancer at each site is calculated from data supplied from renal units treating ESRF patients across Australia and New Zealand. The expected number of cancers is calculated from data supplied to the National Cancer Statistics Clearing House (NCSCH). Individual States and Territories in Australia are required by legislation to maintain a registry of all new cases of cancer in Australian residents. The NCSCH receives data from these cancer registries, and summary data is available from the AIHW website (www.aihw.gov.au/cancer/ncsch/index). Results of these analyses are presented as standardised incidence ratios (SIR) with 95% confidence intervals (CI), which can be interpreted like risk ratios or relative risk; a value of SIR = 1 is equivalent risk, SIR = 0.5 is half the risk, SIR = 2 is double the risk etc. The breadth of the 95% CI reflects the precision of the SIR estimates, and those with 95% CI which do not cross 1 can be regarded as statistically significant

Figure 10.1 shows the risk of cancer experienced by the 33,822 patients undergoing dialysis therapy in Australia and New Zealand between 1980 and 2003, compared to that experienced by the Australian general population. The period of risk for a dialysis patient starts on the day of first dialysis treatment and ends at either (first) transplantation, death or last known follow-up, which ever occurs soonest. Periods of time spent on dialysis after a failed (first) transplant are not considered in this figure (see below). Incident cancers diagnosed at any time after the first day of dialysis are summed in the observed totals. Prior ANZDATA reports have excluded those cancers diagnosed within three months of commencing dialysis therapy, however, for these calculations we opted to include all cancers not known on the date of first dialysis. Site specific cancers are reported in groupings used by the AIHW, and not as previously using those of the South Australian Cancer Registry.

Figure 10.2 shows the risk of cancer experienced by the 13,077 patients who underwent at least one renal transplant in Australia and New Zealand between 1980 and 2003, compared to that experienced by the Australian general population. For these calculations the period of risk for each patient starts on the day of transplantation and continues until death or last known follow-up. Patients have not been removed from the analysis at the time of graft failure as we felt it was important to provide clinicians with an idea of lifetime risk of cancer following transplantation, and also because risk of malignancy is unlikely to return to pre-transplant levels following graft failure. Observed cancers are all those reported at any time after the date of first transplantation, and include those occurring after graft failure, and those that occurred after a subsequent transplant; following a 'once transplanted always transplanted' rule.

The second section of this report examines the cumulative risk of a cancer (excluding non-melanocytic skin cancers) with time for patients with ESRF. Figure 10.3 shows the cumulative risk of at least one cancer (excluding non-melanocytic skin cancer) for those undergoing dialysis therapy in Australia and New Zealand, by time on dialysis. The numbers tabulated below the graph shows the number of patients remaining at risk as time progresses. Dialysis patients cease to be at risk from the day of first transplant, death or last known follow-up, which ever is earlier. Similarly Figure 10.4 shows the lifetime risk of at least one cancer (excluding non-melanocytic skin cancer) following a kidney transplant. Figure 10.5 shows cumulative risk of at least one cancer (excluding non-melanocytic skin cancer) for transplanted patients

whilst their first graft continues to function. For these calculations patients cease to be at risk at graft failure, death or last known follow-up, which ever occurs soonest). For Figures 10.3 to 10.5, the curve for the expected number of cancers (excluding non-melanocytic skin cancer) is calculated from the risk experienced by the general population of the same age and gender distribution.

The third part of this report explores the absolute risk of cancer (excluding non-melanocytic skin cancers) for patients after undergoing their first renal transplant. Using data from all 14,354 recipient patients undergoing a transplant from 1963 – 2003, with median follow-up of 7.0 years (inter-quartile range 2.7-13.2), predictors of post-transplant malignancy (excluding non-melanocytic skin cancer) were investigated. These included age at transplantation, gender, donor source, era of transplantation and primary kidney disease. Each potential predictor was examined alone (univariate analysis) and those that demonstrated a significant relationship with diagnosis of a post-transplant malignancy were entered into a multivariate Cox proportional hazards model, to demonstrate the effect of each predictor after allowing for the effect of other predictors. Results were then stratified by predictors demonstrating significant effect modification, and reported as hazard ratios (HR) with 95% CI. A HR can be interpreted like a risk ratio or relative risk.

Of the 14,354 recipients, 1412 (9.8%) had >=1 non-skin cancer. In univariate analysis there was a significantly increased risk of cancer with increasing age at transplantation (trend P< 0.0001), for females (P < 0.002), cadaveric donors (P < 0.0001), those with primary disease other than diabetes (P= 0.003) and those transplanted after 1985 (P < 0.001). However, when allowing for all effects in the multivariate model, gender, age and primary renal disease were significant predictors of cancer

Figure 10.1

Standardised Incidence Ratios for Cancer Risk (excluding non-melanocytic skin cancer) Experienced by Patients Undergoing Dialysis In Australia and New Zealand, 1980 - 2003.

Analysis of 33,822 Patients (87,039 person-years), Standardised for Age, Gender and Calendar Year with Australian General Population

Site of Cancer	Observed Cancer	Expected Cancer	S.Incidence Ratio	95% Confidence Interval	
All Registrable Cancers	**1469**	**861.91**	**1.70**	**1.62**	**1.79**
Head, Neck and Lip	26	10.73	**2.47**	1.68	3.63
Oesophagus	22	12.16	**1.81**	1.19	2.75
Stomach	32	23.80	**1.34**	0.95	1.90
Small Intestine	9	2.40	**3.76**	1.95	7.22
Colorectal	144	134.11	**1.07**	0.91	1.26
Liver	21	7.43	**2.83**	1.84	4.34
Gallbladder	7	6.44	**1.09**	0.52	2.28
Pancreas	21	19.44	**1.08**	0.70	1.66
Nasal Cavity	3	1.44	**2.08**	0.67	6.46
Larynx	8	8.78	**0.91**	0.46	1.82
Trachea, Bronchus and Lung	186	108.49	**1.71**	1.49	1.98
Other Thoracic Organs	3	0.74	**4.04**	1.30	12.51
Bone and Articular Cartilage	4	1.01	**3.95**	1.48	10.53
Melanoma	88	71.18	**1.24**	1.00	1.52
Mesothelioma	11	5.72	**1.92**	1.07	3.47
Kaposi's Sarcoma	8	0.76	**10.46**	5.23	20.92
Connective and Other Soft Tissue	6	5.33	**1.13**	0.51	2.51
Breast	124	84.75	**1.46**	1.23	1.75
Vulva	6	1.49	**4.02**	1.81	8.96
Vagina	3	0.50	**6.05**	1.95	18.76
Cervix Uteri	20	6.64	**3.01**	1.94	4.67
Corpus Uteri	15	13.72	**1.09**	0.66	1.81
Ovary	13	10.16	**1.28**	0.74	2.20
Other Female Genital Organs	0	0.44	**0.00**	-	-
Penis and Other Male Genital Organs	2	1.05	**1.90**	0.48	7.60
Prostate	89	143.77	**0.62**	0.50	0.76
Testis	0	2.00	**0.00**	-	-
Kidney, Ureter and Urethra	197	24.74	**7.96**	6.93	9.16
Bladder	120	35.36	**3.39**	2.84	4.06
Eye	0	2.13	**0.00**	-	-
Brain and Central Nervous System	22	12.25	**1.80**	1.18	2.73
Thyroid Gland	33	5.48	**6.02**	4.28	8.47
Other Endocrine Glands	4	0.45	**8.82**	3.31	23.50
Unknown Primary Site	65	34.32	**1.89**	1.49	2.42
All Lymphomas	48	34.18	**1.40**	1.06	1.86
Immunoproliferative Neoplasms	3	0.68	**4.44**	1.43	13.78
Multiple Myeloma	89	10.97	**8.11**	6.59	9.98
Leukaemias	17	21.85	**0.78**	0.48	1.25

Figure 10.2

Standardised Incidence Ratios for Cancer Risk (excluding non-melanocytic skin cancer) Experienced by Patients Undergoing at Least One Kidney Transplant in Australia and New Zealand 1980 - 2003

Analysis of 13,077 Patients (110,395 person years), Standardised for Age, Gender and Calendar Year with Australian Population

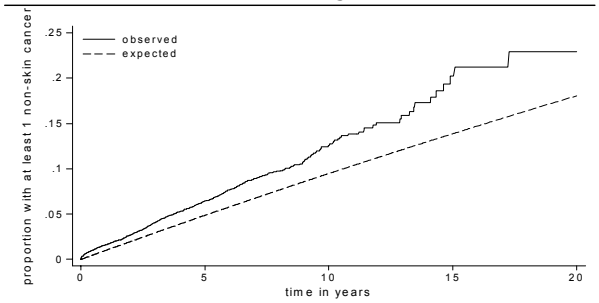
Site of Cancer	Observed Cancer	Expected Cancer	S. Incidence Ratio	95% Confidence Interval	
All Registrable Cancers	**1545**	**495.08**	**3.12**	**2.97**	**3.28**
Head, Neck and Lip	63	22.77	**2.77**	2.16	3.54
Oesophagus	29	6.14	**4.73**	3.28	6.80
Stomach	15	12.07	**1.24**	0.75	2.06
Small Intestine	3	1.49	**2.01**	0.65	6.23
Colorectal	141	72.76	**1.94**	1.64	2.29
Liver	19	3.97	**4.78**	3.05	7.49
Gallbladder	8	3.21	**2.49**	1.25	4.98
Pancreas	16	9.30	**1.72**	1.05	2.81
Nasal Cavity	5	0.92	**5.41**	2.25	13.00
Larynx	11	5.54	**1.99**	1.10	3.59
Trachea, Bronchus and Lung	108	53.85	**2.01**	1.66	2.42
Other Thoracic Organs	6	0.57	**10.60**	4.76	23.60
Bone and Articular Cartilage	5	1.01	**4.94**	2.06	11.87
Melanoma	183	57.64	**3.18**	2.75	3.67
Mesothelioma	4	2.97	**1.35**	0.51	3.59
Kaposi's Sarcoma	28	1.06	**26.44**	18.26	38.29
Connective and Other Soft Tissue	12	3.80	**3.16**	1.79	5.56
Breast	87	69.52	**1.25**	1.01	1.54
Vulva	41	0.90	**45.60**	33.58	61.93
Vagina	12	0.33	**36.02**	20.46	63.43
Cervix Uteri	46	6.97	**6.60**	4.94	8.81
Corpus Uteri	18	9.75	**1.85**	1.16	2.93
Ovary	8	7.56	**1.06**	0.53	2.12
Other Female Genital Organs	0	0.32	**0.00**	-	-
Penis and Other Male Genital Organs	11	0.62	**17.81**	9.86	32.16
Prostate	53	54.72	**0.97**	0.74	1.27
Testis	0	4.36	**0.00**	-	-
Kidney, Ureter and Urethra	125	14.73	**8.49**	7.12	10.12
Bladder	82	15.97	**5.14**	4.14	6.38
Eye	4	1.50	**2.67**	1.00	7.12
Brain and Central Nervous System	16	9.59	**1.67**	1.02	2.72
Thyroid Gland	27	5.96	**4.53**	3.11	6.61
Other Endocrine Glands	4	0.43	**9.37**	3.52	24.97
Unknown Primary Site	70	16.74	**4.18**	3.31	5.28
All Lymphomas	231	22.74	**10.16**	8.93	11.55
Immunoproliferative Neoplasms	3	0.29	**10.23**	3.30	31.73
Multiple Myeloma	15	5.62	**2.67**	1.61	4.42
Leukaemia	32	12.28	**2.61**	1.84	3.69

but both donor source (P = 0.25) and era (P = 0.87) were not. There was strong evidence of interaction between age and gender (P = 0.02), meaning that the effect of gender on cancer risk varied depending on age at transplantation, and that at different ages, the difference between risk for each gender would not be constant. For men compared to women <35 years at transplantation HR 0.78 (0.63-0.96), 35-44 years HR 0.75 (0.60-0.93), 45-54 years HR 1.00 (0.81-1.22) and >=55 years HR 1.13 (0.90-1.40).

Figure 10.6 summarises the results of this analysis, aiming to give clinicians a clear estimate of a patient's risk of developing a cancer (excluding non-melanocytic skin cancer) by gender and age at transplantation. This information should be useful for pre-transplant counselling, and to enable clinicians to identify those groups at higher risk of developing a malignancy.

Figure 10.3

Cumulative Risk of at Least One Cancer (Excluding Non-Melanocytic Skin Cancer) Whilst on Dialysis

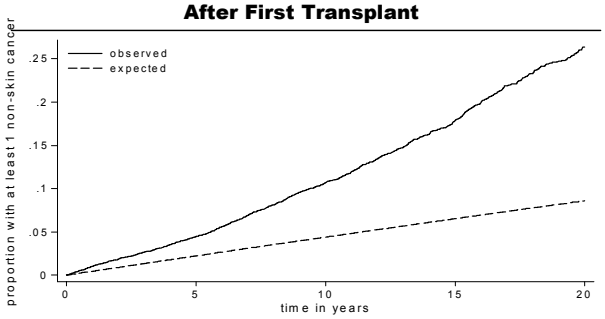


At risk	37791	5003	633	87	18

Patients become at risk at time of first dialysis treatment, and cease to be at risk at time of first transplant, death or last known follow-up. Expected curve is calculated for a general population of the same age and sex distribution

Figure 10.4

Lifetime Cumulative Risk of at Least One Cancer (Excluding Non-Melanocytic Skin Cancer) After First Transplant

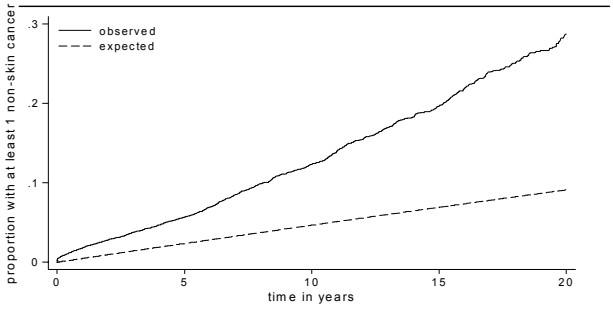


At risk	12456	8531	5020	2600	1192

Patients become at risk at time of first transplant, and cease to be at risk at time of death or last known follow-up. Expected curve is calculated for a general population of the same age and sex distribution

Figure 10.5

Cumulative Risk of at Least One Cancer (Excluding Non-Melanocytic Skin Cancer) Whilst Graft Continues to Function



At risk	12456	6238	3079	1279	487

Patients become at risk at time of first transplant, and cease to be at risk at time of graft failure, death or last known follow-up. Expected curve is calculated for a general population of the same age and sex distribution

Figure 10.6

Absolute Cancer Risk in the Clinical Setting. Adjusted risk of >=1 cancer (excluding non-melanocytic skin cancer) By time after First Kidney Transplant

Years since Transplant	Risk of Non-skin Cancer by age at Transplantation (%)							
	<35 years		35-44 years		45-54 years		>= 55 years	
	Male	Female	Male	Female	Male	Female	Male	Female
5	1.3	2.1	3.1	3.7	5.7	6.8	10.1	9.6
10	4.2	5.8	7.5	9.6	14.4	14.7	24.6	20.9