CHAPTER 10

CANCER REPORT

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INTRODUCTION

UNDERSTANDING CANCER RISK IN ESKD

Recent ANZDATA cancer reports have concentrated on elaborating cancer risk in the ESKD population of Australia and New Zealand and examining the validity of different approaches to recording cancer and calculating cancer risk estimates. This year's report concentrates on applying risk estimates to individual patients and on implications this may have for that patient's care.

There are two aims for this year's cancer report: to quantify how excess cancer risk varies within the transplanted population, relative to the general population and also in absolute terms for different patients with a kidney transplant and to investigate cancer screening strategies for two common cancers in dialysis (breast cancer) and transplanted (colorectal cancer) ESKD populations.

Relative and absolute risks of cancer for kidney recipients in Australia and New Zealand.

It is clear that renal transplant recipients have increased cancer risk at almost all sites, but data on risk variation across different patient groups have been sparse.

Quantifying an individual transplant candidate's cancer risk informs pre-transplant counselling, subsequent treatment decisions and has implications for monitoring, screening and follow-up after transplantation. Most previous published analyses of cancer risk after transplantation have concentrated on specific cancers, or on risk associated with modifiable factors after the fact of transplantation, such as particular components of the immunosuppressive regimen employed. However, immunosuppressive therapy choices happen after the fact of transplantation, whereas a large proportion of cancer risk depends on recipient characteristics that are unalterable and evident before the fact of transplantation.

This year we published an analysis of relative and absolute cancer risk for different patient groups: Webster AC, Craig JC, Simpson JM, Jones MP, Chapman JR Identifying high risk groups and quantifying absolute risk of cancer after kidney transplantation: a cohort study of 15,183 recipients. *Am J Transplant*. 2007;7 (9):2140-51. (1) The key findings are summarised here.

Using data from the Australian Institute of Health and Welfare and the New Zealand Health Information Service, we compared the risk of common cancers in kidney recipients by age and gender over the calendar years 1980–2002. During this period 12,633 transplant recipients records were analysed, representing 104,084 years at risk, during which time 1,324 (10.5%) developed at least one new cancer (excluding non-melanocytic skin and lip cancer).

For both genders and at all ages, the rates of cancer were similar to non-transplanted people 20-30 years older. A female transplant recipient aged 25 experienced a rate of cancer equivalent to a 55 year old woman in the general population (779.2/100,000 compared with 776.8/100,000 respectively) and a 45 year old female recipient experienced a rate equivalent to a 70 year old female (1458.9/100,000 compared with 1408.7/100,000 respectively). For males the situation was similar, with 30 year old recipients experiencing a rate of 435.5/100.000, similar to a 50 year old male in the general population (458.8/100,000).

Risk varied by cancer site. Figure 10.1 shows relative risk of cancers by age and gender for the most common cancers in the general population (colorectal, lung, melanoma, breast and prostate) and the most common cancer in the transplant population: lymphoma (classified in the general and transplanted populations to include Hodgkin's and non-Hodgkin's lymphoma).

For colorectal cancer in both genders, risk followed the observed overall age trend and was greatest for younger patients, falling with age, with a similar trend for breast and lung cancer. The same pattern occurred for lymphoma, although the magnitude of risk remained considerably higher. In contrast, elevated risk of melanoma for males and females showed less variability across ages and prostate cancer was not significantly increased at all.

While there is established literature on prediction of risk of cardiovascular disease after transplantation and a growing number of studies aiming to risk stratify for post-transplant diabetes, there is far less published on variation in malignancy risk, despite the fact that almost as many recipients die with a functioning graft from cancers, as do from cardiovascular causes.

Using survival analysis methodology the absolute risk of cancer within transplanted population was modelled for all recipients from 1963-2004. The analysis was limited to unmodifiable cancer risk factors known to clinicians and patients at the time of transplantation; age, gender, primary underlying cause of ESKD, racial background, history of prior non-skin malignancy. To allow for the uncertainty of on-going graft function over time, we also included graft failure in the model.

Figure 10.1

Site-specific Cancer Risk for Kidney Transplant Recipients by Age and Gender for Common Cancers

Age at Cancer Diagnosis	<35 years			35-44 years			45-54 ears			>=55 years		
	O	E *	SIR (95% CI)	O	E *	SIR (95% CI)	O *	E *	SIR (95% CI)	O *	E *	SIR (95% CI)
Female												
Breast	4	1.28	3.12 (1.17, 8.31)	11	7.80	1.41 (0.78, 2.51)	30	19.23	1.56 (1.08, 2.21)	34	37.31	0.91 (0.65, 1.27)
Colorectal	3	0.22	13.51 (4.34, 41.61)	8	1.16	6.88 (3.44, 13.75)	18	4.91	3.66 (2.31, 5.82)	45	19.88	2.26 (1.69, 3.03)
Melanoma	6	1.90	3.17 (1.42, 7.04)	7	3.25	2.46 (1.23, 4.93)	18	4.90	3.88 (2.47, 6.08)	33	8.93	3.70 (2.63, 5.20)
Lung	0	0.04	-	0	0.38	-	8	1.97	4.06 (2.03, 8.11)	30	10.08	2.98 (2.08, 4.26)
Lymphoma †	19	0.51	37.30 (23.79, 58.48)	11	0.75	14.67 (8.13, 26.50)	16	1.61	9.95 (6.09, 16.24)	33	5.23	6.30 (4.48, 8.87)
Male												
Prostate	0	0.00	-	0	0.13	-	2	4.02	0.50 (0.12, 1.98)	43	47.87	0.90 (0.64, 1.20)
Colorectal	0	0.33	-	13	1.93	6.73 (3.91, 11.60)	11	8.67	1.27 (0.70, 2.29)	37	33.14	1.12 (0.81, 1.54)
Lung	1	0.08	11.81 (1.66, 83.83)	4	0.80	5.03 (1.89, 13.39)	13	5.45	2.39 (1.39, 4.11)	48	27.85	1.72 (1.30, 2.29)
Melanoma	10	2.13	4.69 (2.53, 8.72)	20	4.57	4.38 (2.82, 6.79)	23	8.34	2.74 (1.82, 4.12)	46	15.54	3.15 (2.38, 4.17)
Lymphoma †	25	1.09	23.03 (15.56, 34.09)	23	1.85	12.43 (8.26, 18.71)	31	3.42	9.06 (6.37, 12.88)	50	7.57	6.61 (5.01, 8.72)

O = observed incident cancers, in ANZDATA cohort, between 1980-2002

E = expected number of incident cancers in Australian and New Zealand general population of the same age and sex distribution, occurring over the same calendar years

SIR = standardised incidence ratio

† Lymphoma classified in the general and transplanted populations to include Hodgkins and non-Hodgkin's lymphoma. Comparison is made only with incidence in the Australian general population as comparable Lymphoma data was not available for New Zealand.

Based on a table originally published in Webster et al. Am J Transplant. 2007;7(9):2140-51.

UNDERSTANDING CANCER RISK IN ESKD (CONTINUED)

The absolute risk estimates presented in Figure 10.2 aim to provide clinicians and patients with a reference table to stratify the likelihood of being diagnosed with malignancy after transplantation through a clear risk estimate appropriate to their individual situation, rather than the more generalised estimates available until now. Where one in 14 white women transplanted before the age of 35 with glomerulonephritis causing ESKD, no prior history of a cancer and a graft functioning for ten years can expect a cancer, this rises to one in three white men with a prior history of cancer transplanted aged 55 or over, but with ESKD from the same cause. Similarly, men aged 45-54 at transplantation with graft function at ten years have cancer risks varying from one in 13 (non-white, diabetic ESKD, no prior cancer) to one in five (white, prior cancer, ESKD from other causes).

Cancer screening in the renal transplant and dialysis population

Population screening for breast, colorectal and cervical cancers are now standard practice in the general population of most developed countries. There is now evidence from good randomised controlled trials and observational studies confirming breast, colorectal and cervical cancer screening in the general population reduces cancer specific mortality.(2-4). Mammography, faecal occult blood testing (FOBT) and Pap smear are accurate screening tools with the test specificities and sensitivities exceed over 80-90%.(5-8). Population breast, colorectal and cervical cancer screening programs have been shown to be cost-effective with the benefits of screening exceed the perceived harms in the general population (9-11).

Despite the increase in overall cancer risk that we have demonstrated, there is a paucity of trial-based evidence to assess the survival benefits, test accuracy and potential harms of cancer screening in the end-stage kidney disease and renal transplant populations.

Previous cost-effective analyses have shown that cancer screening is unlikely to provide any survival benefits in individuals with average cancer risks in the dialysis and transplant population because of competing risks of death from causes other than cancers. (12;13).

Others have refuted this argument and stated cancer screening is underused and efforts should be made to improve the overall screening rate. (14).

In the absence of good quality trial-based evidence, considerable uncertainty exists as to whether the standard methods for early detection of cancers in the general population offer similar survival benefits in the ESKD and transplant population, when the overall age-specific mortality rates are exceedingly higher than the general population.

In this report, we have provided two cost-effectiveness analyses estimating both the costs and health outcomes of breast and colorectal cancer screening in the dialysis and renal transplant populations using decision analytical modelling.

Figure 10.2

Absolute Risk of Cancer Diagnosis: Expected Cases per 100 Kidney Recipients (%) At 1, 5 and 10 Years After Transplantation for Different Patient Groups

Primary Renal Disease	Racial Background	Prior Cancer History	Graft Function	Age at Transplantation <35 Years						Age at Transplantation 35-44 Years					
				One Year		Five Years		Ten Years		One Year		Five Years		Ten Years	
				F	M	F	M	F	M	F	M	F	M	F	M
GN/IgA	White	No	Yes	0.7	0.5	3.0	2.1	7.3	5.2	1.2	0.8	5.4	3.6	12.7	9.5
			Failed	0.6	0.4	2.7	1.9	6.4	4.8	1.1	0.8	4.7	3.4	11.2	8.5
		Cancer	Yes	0.9	0.7	4.2	3.0	10.0	7.5	1.2	1.2	7.4	5.3	17.3	13.2
			Failed	0.8	0.6	3.7	2.6	8.8	6.6	1.5	1.1	6.5	4.7	15.3	11.7
	Non-white	No	Yes	0.5	0.4	2.1	1.6	5.2	4.0	0.8	0.6	3.7	2.8	9.3	7.2
			Failed	0.4	0.3	2.0	1.3	4.7	3.4	0.8	0.5	3.5	2.5	8.4	6.4
		Cancer	Yes	0.7	0.5	3.1	2.2	7.5	5.6	1.3	0.9	5.5	4.0	13.0	9.9
			Failed	0.6	0.4	2.7	1.9	6.6	4.9	1.1	0.5	4.8	3.5	11.5	8.8
Other	White	No	Yes	0.6	0.4	2.8	2.0	6.8	4.9	1.1	0.8	5.0	3.6	11.9	9.0
			Failed	0.6	0.4	2.5	1.7	6.0	4.4	1.0	0.7	4.4	3.1	10.4	7.9
		Cancer	Yes	0.9	0.6	3.9	2.8	9.4	7.0	1.6	1.1	6.9	4.9	16.2	12.3
			Failed	0.7	0.5	3.4	2.4	8.2	6.1	1.4	0.9	6.1	4.4	14.3	10.9
	Non-white	No	Yes	0.5	0.3	2.1	1.5	5.0	3.7	0.8	0.6	3.7	2.6	8.9	6.7
			Failed	0.4	0.3	1.8	1.3	4.4	3.3	0.7	0.5	3.2	2.3	7.8	5.9
		Cancer	Yes	0.7	0.5	2.9	2.0	7.0	5.2	1.2	0.8	5.1	3.7	12.2	9.2
			Failed	0.6	0.4	2.5	1.8	6.1	4.6	1.0	0.7	4.5	3.2	10.7	8.1
DM	White	No	Yes	0.5	0.3	2.1	1.4	5.0	3.6	0.8	0.6	3.7	2.6	8.8	6.6
			Failed	0.4	0.3	1.8	1.3	4.4	3.2	0.7	0.5	3.2	2.3	7.7	5.8
		Cancer	Yes	0.6	0.5	2.9	2.0	6.9	5.1	1.1	0.8	5.1	3.6	12.0	9.1
			Failed	0.6	0.4	2.5	1.8	6.0	4.5	1.0	0.7	4.4	3.2	10.6	8.0
	Non-white	No	Yes	0.3	0.2	1.5	1.1	3.7	2.7	0.6	0.4	2.7	1.9	6.5	4.9
			Failed	0.3	0.2	1.3	0.9	3.2	2.4	0.5	0.4	2.4	1.7	5.7	4.3
		Cancer	Yes	0.5	0.3	2.1	1.5	5.1	3.8	0.8	0.6	3.8	2.7	9.0	6.8
			Failed	0.4	0.3	1.8	1.3	4.5	3.3	0.7	0.5	3.3	2.4	7.9	6.0
				Age at Transplantation 45-54 years						Age at Transplantation >=55years					
GN/IgA	White	No	Yes	1.5	1.4	6.5	6.2	15.2	15.4	2.2	2.5	9.7	10.6	22.3	25.1
			Failed	1.3	1.3	5.7	5.5	13.4	13.6	2.0	2.2	8.6	9.3	19.8	22.4
		Cancer	Yes	2.1	2.0	9.0	8.6	20.6	20.8	3.1	3.4	20.3	14.0	29.7	33.2
			Failed	1.8	1.7	7.9	7.6	18.3	18.4	2.7	3.0	11.8	12.9	26.5	30.1
	Non-white	No	Yes	1.1	1.1	4.8	4.6	11.4	11.6	1.7	1.8	7.2	7.9	16.9	19.2
			Failed	1.0	0.9	4.2	4.1	10.1	10.2	1.4	1.6	6.4	7.0	14.9	17.1
		Cancer	Yes	1.5	1.4	6.7	6.4	15.6	15.8	2.3	2.5	10.0	10.8	22.8	25.7
			Failed	1.3	1.3	5.8	5.6	13.8	14.0	2.0	2.2	8.8	9.6	20.2	23.1
Other	White	No	Yes	1.4	1.3	6.0	5.8	14.2	14.3	2.1	2.3	9.1	9.8	20.9	23.5
			Failed	1.2	1.1	5.3	5.1	12.5	12.7	1.8	2.0	8.0	8.7	18.5	21.1
		Cancer	Yes	1.9	1.8	8.3	8.0	19.3	19.4	2.9	3.2	12.5	13.4	27.9	31.2
			Failed	1.7	1.6	7.3	7.1	17.1	17.2	2.5	2.8	11.0	11.9	24.9	28.2
	Non-white	No	Yes	1.0	1.0	4.5	4.3	10.7	10.8	1.5	1.7	6.7	7.3	15.8	17.9
			Failed	0.9	0.9	3.9	3.8	9.4	9.5	0.3	1.5	5.9	6.5	14.0	15.9
		Cancer	Yes	1.4	1.4	6.2	6.0	14.6	14.7	2.1	2.3	9.3	10.1	21.4	24.1
			Failed	1.2	1.2	5.4	5.2	12.9	13.0	1.9	2.0	8.2	8.9	19.0	21.6
DM	White	No	Yes	1.0	1.0	4.4	4.2	10.5	10.6	1.5	1.6	6.7	7.2	15.6	17.7
			Failed	0.9	0.8	3.9	3.7	9.3	9.4	0.3	1.5	5.9	6.4	13.8	15.7
		Cancer	Yes	1.4	1.3	6.1	5.9	14.4	14.5	2.1	2.3	9.2	9.9	21.1	23.9
			Failed	1.2	1.2	5.4	5.2	12.7	12.8	1.9	2.0	8.1	8.8	18.7	21.4
	Non-white	No	Yes	0.7	0.7	3.3	3.1	7.9	7.9	1.1	1.2	4.9	5.4	11.7	13.3
			Failed	0.6	0.6	2.9	2.8	6.9	7.0	1.0	1.1	4.3	4.7	10.3	11.9
		Cancer	Yes	1.0	1.0	4.5	4.4	10.8	10.9	1.6	1.7	6.8	7.4	16.0	18.1
			Failed	0.9	0.9	4.0	3.8	9.5	9.6	1.4	1.5	6.0	6.5	14.1	16.2

UNDERSTANDING CANCER RISK IN ESKD (CONTINUED)

Breast cancer screening in the dialysis population

A deterministic Markov model was developed to simulate the natural history of progression of breast cancer in a hypothetical cohort of women ages 50-69 on dialysis over time using data obtained from the ANZDATA Registry (1995-2006) and information extrapolated from the general population. Outcomes of the model included average costs, in Australian dollars, health benefits, measured in life years saved (LYS), and the incremental cost-effectiveness ratio of screening compared to no screening. The incremental cost-effectiveness ratio (ICER) is calculated using the following formula:

$$ICER = \frac{Cost_{New} - Cost_{Comparator}}{Effectiven\ ess_{New} - Effectiven\ ess_{Comparator}}$$

Where new are the screened and comparator are the unscreened populations.

All costs and benefits are also discounted using a recommended discount rate of 5% per annum. A simplified structure of the model is shown in Figure 10.3. To determine the robustness of the analysis, we also tested the extent to which this model's assumptions were sensitive to the uncertainties within the variables using one-way sensitivity analyses.

Assuming a participation rate of 50%, and the starting age at 50, the total costs of screening is $4,353 compared to the costs of no screening of $4,004. The extra costs of screening are $350. The total benefits of screening are 5.67552 LYS compared to 5.56326 LYS of no screening. The extra benefits of screening are 0.00226 LYS, which is equivalent to 0.83 days of lives saved. The incremental cost-effectiveness ratio of annual mammographic screening in women on dialysis compare to no screening is $154,783/LYS.

When a series of one-way sensitivity analyses were performed, the model was most sensitive to changes in the following: test specificity, participation rate, prognosis and survival post treatment, prevalence of disease and the costs of mammography.

Figure 10.4 shows results of the one-way sensitivity analyses. The vertical line represents the ICER, $154,783/LYS, at base-case analysis. Despite varying between the very best and worst estimates, the ICER remains high and above the acceptable cost-effectiveness ratio, suggesting that even under the most favourable conditions, population breast cancer screening in women with ESKD on dialysis is unlikely to be cost-effective. We are not achieving the comparable survival benefits from screening in the dialysis population because of the reduced overall life expectancy and the increased number of excess deaths from causes other than cancer.

The appropriate approach to screening may therefore be stratified according to the individual's risk, life expectancy and quality of life.

Colorectal cancer screening in the renal transplant populations

A similar model was also constructed in a cohort of renal transplant recipients aged between 50 and 70, comparing the cost-effectiveness of annual immunochemical faecal occult blood testing against no screening using updated data from the ANZDATA registry (1995-2006) and information from the general population. Figure 10.3 shows the simplified structure of the colorectal cancer model.

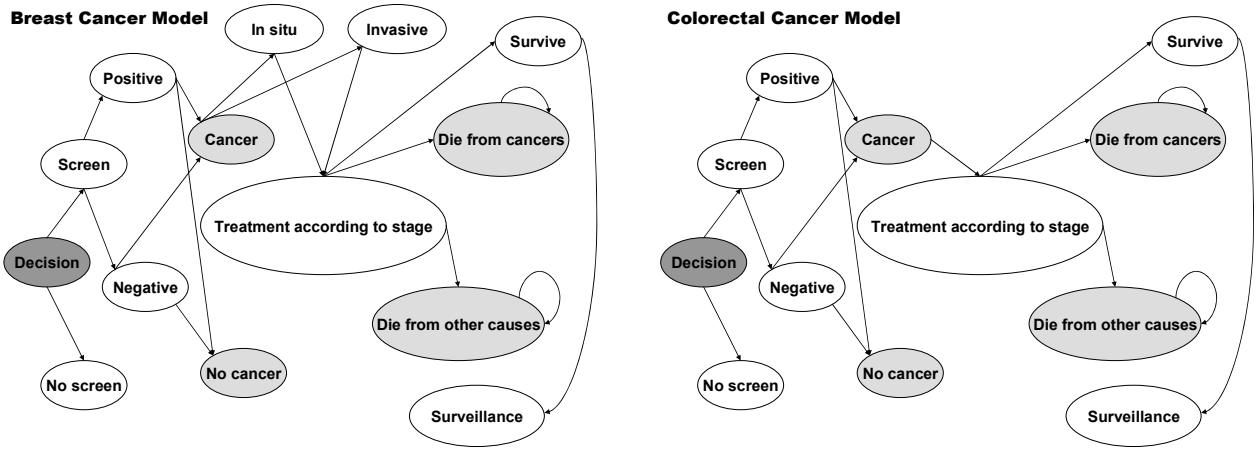
Assuming a participation of 50%, and the starting age at 50, the average costs for annual FOBT was $5,076 comparing to the costs of no screening of $3,606. The total benefits in life years are 7.851 life years for screening and 7.917 life years for no screening. The incremental benefits are 0.067 LYS, which is equivalent to 24 days of lives saved in the screened population. The overall incremental cost-effectiveness ratio of annual IFOBT is $22,309/LYS. The model was robust to changes in the following variables over the range tested in sensitivity analyses: test specificity, prevalence of disease, test specificity and participation of the program. For example if we varied the test specificity from 0.35 to 0.95, the ICER varies between an acceptable values of $2,857/LYS to an ineffective ratio of $81,718/LYS.

It may therefore be attractive to screen under the best assumptions, but clinicians should be aware of the uncertainty inherent in the base-case results when making decisions about colorectal cancer screening in renal transplant recipients.

Colorectal cancer screening in the renal transplant population may appear cost-effective if all assumptions are made under the most favourable conditions. Our study suggests that primary studies evaluating some of the more influential variables in our model such as the test performance of FOBT for the detection of colorectal cancer, along with better information about the likely pattern of stage shift with screening and the quality of life of patients with cancers will resolve some of the key residual uncertainties about the effects and costs of screening in the renal transplant population.

Figure 10.3

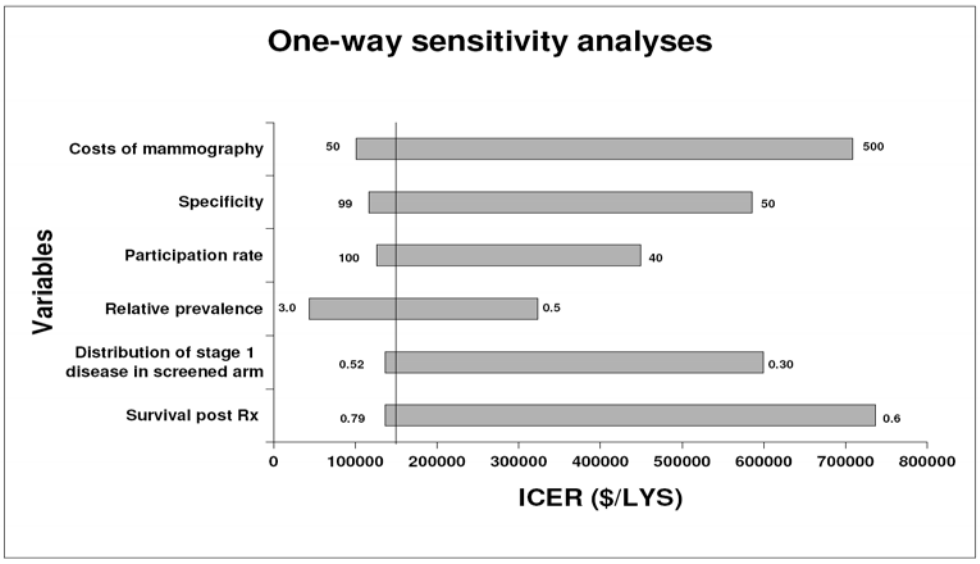
Simplified Structure of the Breast and Colorectal Cancers Models*



* Ovals in light grey represent data obtained from the ANZDATA Registry (1995-2006)
Ovals in white represent data extrapolated from the general population

Figure 10.4

One-way Sensitivity Analyses of the Breast Cancer



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