Original Articles

Health benefits and costs of screening for colorectal cancer in people on dialysis or who have received a kidney transplant

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ABSTRACT

Background. Despite the higher risk of colorectal cancer (CRC) in people with chronic kidney disease, it remains uncertain whether early detection through screening is cost-effective in this setting. We aimed to determine the costs and health benefits of CRC screening in people on dialysis or who have received a kidney transplant.

Methods. Using a government health perspective, three probabilistic Markov models were constructed to compare the cost-effectiveness and cost-utility of annual immunochemical faecal occult blood test (iFOBT) screening against no-screening in a cohort of 1000 patients (age 50–70 years) on dialysis and with kidney transplants. A series of one-way, multi-way and probabilistic sensitivity analyses were conducted to assess the robustness of the model structure and the extent in which the model's assumptions were sensitive to the uncertainties within the input variables.

Results. The incremental cost-effectiveness ratios (ICERs) of CRC screening compared with no-screening were $138 828 per quality-adjusted life year [QALY; $122 977 per life year

saved (LYS)], $121 973 per QALY ($ 85 095 per LYS) and $44 790 per QALY ($25 036 per LYS) for dialysis patients not listed on the transplant waiting list, patients on the transplant waiting list and patients with kidney transplants, respectively. The test specificity of iFOBT, the starting age of screening and cancer prevalence were influential factors that determined the overall cost-effectiveness of screening in this setting.

Conclusion. Screening for CRC using iFOBT may reduce cancer-specific mortality in patients on dialysis and with kidney transplants. However, the benefits and costs of screening CRCs in patients on dialysis, especially for those deemed not suitable for transplantation, greatly exceeded the typical thresholds for acceptable cost-effectiveness.

INTRODUCTION

Colorectal cancer (CRC) will soon surpass lung cancer as the leading cause of death due to cancer in the Western world [1, 2]. Screening for CRC is now standard clinical practice in most developed countries, because there is high quality

evidence to suggest early cancer detection through screening and the subsequent resection of pre-cancerous polyps reduces cancer-specific mortality in the general population [3–5]. Faecal occult blood testing (FOBT) is the most commonly used screening tool and has the strongest trial base for mortality benefits in the general population [6–11]. Screening for CRC using immunochemical FOBT (iFOBT) (also known as faecal immunohistochemical test) is also cost-effective [3], reasonably accurate [4, 5], well-tolerated and acceptable by the general community [12, 13].

The costs and consequences of screening in people with chronic kidney disease (CKD) is likely to be different. Screening using iFOBT in CKD may incur a greater risk of false-positive results because of minute gastrointestinal bleeding from dysfunctional platelets secondary to uraemia, a higher risk of colonic angiodysplasia and the greater use of anti-platelets and anti-coagulants during dialysis [14–16]. The harms of subsequent testing may also be greater. People with CKD may be more susceptible to electrolyte derangement during bowel preparation, and more likely to have colonoscopy- and polypectomy-related complications such as sedation-related events, perforation and postpolypectomy bleeding [17, 18]. In addition, over-detection of inconsequential disease may carry financial and health burdens, which will adversely impact the patient's quality of life.

Unlike for the general population, there are no randomized controlled trials of CRC screening in people with CKD, and such trials will probably never be done because of limited feasibility. Previous studies have examined the likely impact of CRC screening in the transplanted setting using modelled analyses [19, 20], but did not assess the benefits and the quality of life impact of screening in other non-transplanted CKD populations. In this study, we aim to estimate the health outcomes [in both life years and quality-adjusted life years (QALYs)] and costs of screening CRC in the dialysis and kidney transplant populations.

MATERIALS AND METHODS

Using a government payer perspective, three probabilistic Markov models were constructed to simulate the natural history of screening for CRC in hypothetical cohorts of kidney transplant recipients, dialysis patients on the transplant waiting list and dialysis patients who were not on the transplant waiting list ($n = 1000$). The models included all the potential consequences of screening, the diagnostic procedures and the treatment of CRC in kidney transplant recipients and patients on dialysis. We populated the models using the best available evidence and tested the uncertainties within the input variables and the model structures using one-way and probabilistic sensitivity analyses.

Model structure

Full details of the model structure are published elsewhere [19]. In brief, three different analyses were conducted to compare the health benefits and costs of iFOBT screening with no screening in the three different populations: dialysis patients not on the transplant waiting list, dialysis patients on the transplant waiting and the kidney transplant populations. Further refinements of the previously published models were made [4] that took into consideration the events that followed transplant failures such as returned to dialysis and the possibility of receiving another live donor or deceased donor transplant. A schematic representation of our model for the listed dialysis population is shown in Figure 1. The screening and diagnostic pathways for dialysis patients not listed on the transplant waiting list and kidney transplant recipients were similar to those on the transplant waiting list. However, we assumed that all dialysis patients not listed on the transplant waiting list would not have the chance of receiving a transplant.

Patients had the choice of receiving screening or no screening. Those who received screening and were screened positive underwent colonoscopy. In the no-screening arm, cancers could only be diagnosed clinically. Patients with undiagnosed cancers either survived with the disease undiagnosed, died with the disease undiagnosed or died from other causes. Our model also took into consideration the potential complications of diagnostic colonoscopies such as colonic bleeding and perforations.

Of those diagnosed with CRCs, treatment modality was dependent on the cancer stage at the time of diagnosis. Individuals with localized CRCs without lymph node involvement received surgical management only, whereas those with lymph node involvement received surgical and adjuvant therapy. Adjuvant therapy included chemotherapy, radiotherapy or a combination of both. Patients with widespread metastatic disease received palliative care only.

Patients who were cured from their CRCs were shifted to the surveillance pool, where annual colonoscopies were conducted for the first 2-year post-operative period and then every 5 years hence. Any cancer recurrences were detected through surveillance colonoscopies or clinical diagnoses. Dialysis patients on the waiting list with previously diagnosed CRCs were eligible for transplantation after a cancer-free period of 5 years. Patients without cancers and remained alive at the end of year one returned to the beginning of the screening/no-screening decision node. At the end of each annual cycle, dialysis patients who were not on the waiting list survived on dialysis with or without cancer, or died from cardiovascular disease and/or other causes. Dialysis patients who were on the transplant waiting list survived on dialysis with or without cancers, received a transplant, or died from cardiovascular disease and/or other causes.

Transplanted patients survived with or without cancers, experienced transplant graft failure and returned to dialysis, or died from cardiovascular disease and/or other causes. At the end of each annual cycle, the costs and health benefits of each individual were accrued for the specific health state and the cumulative costs and health benefits were estimated over the lifetime of the patients. We assumed screening stopped at aged 74 years. The model terminated when all patients were deceased. All future costs and benefits were discounted at a rate of 5% per annum. Half-cycle corrections were used and all modelling was conducted using TreeAge Pro Suite 2009 (TreeAge software, Williamstown, MA) and Excel Microsoft[*].
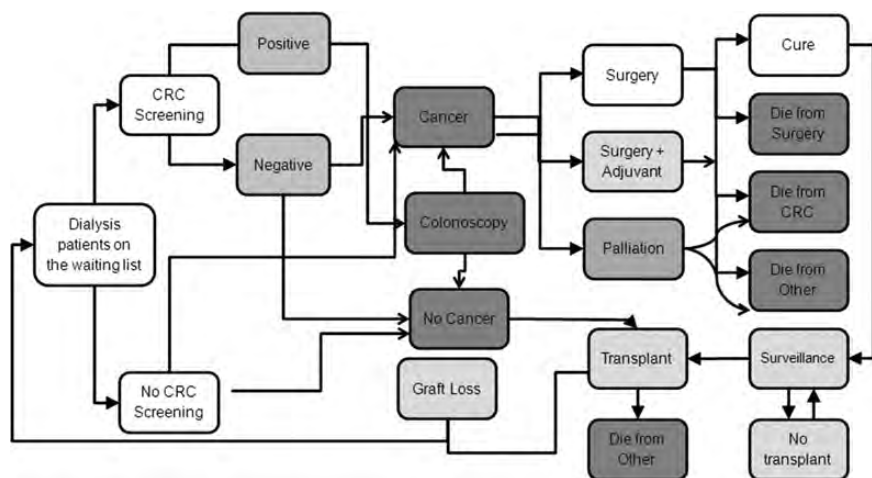
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FIGURE 1: Schematic diagram of screening CRC in dialysis patients on the transplant waiting list.

Input parameters for the model

Clinical data (Appendix 1). Information on the age-specific CRC prevalence for the general population [2] was adjusted for dialysis and transplant patients by a factor of 1.25 and 2.5, respectively [21, 22]. The CRC stage distributions at diagnosis [6, 8, 11, 23] and stage-specific survival [7, 9, 23, 24] of screened and unscreened individuals, the incidence of cancer relapse [25–27] and the iFOBT test performance [4] for the transplanted and dialysis populations were extrapolated from published data for the general population. Information on all-cause mortality of dialysis patients, probability of receiving transplant and graft loss were extrapolated from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) [21]. Utility-based quality-of-life estimates for the various stages of CRC in CKD were based on a recently published study in the Australian CKD population [28]. The treatment and management of stage-specific CRCs was sourced from current recommended clinical practice guidelines [29].

Costs data (Appendix 2). Only direct health care costs were used in the analyses. Unit costs of CRC screening and treatment were obtained from the Australian Refined Diagnosis Related Groups (AR-DRG), the Australian Medicare Benefits Schedule, Cancer Institute of New South Wales and the Australian Institute of Health and Welfare [3, 30–32].

Sensitivity analysis

Assumptions were tested over a range of plausible values to assess the robustness of the uncertainties in the model's parameters using sensitivity analysis. Using one-way sensitivity analysis, we identified all the influential variables within the model. Probabilistic sensitivity analysis was also undertaken. Instead of using point estimates for parameter values, this approach assigns a distribution to each model parameter and samples from that distribution using Monte Carlo simulation to estimate the expected value of each option. We used log-normal distributions for relative risks, beta distributions

for utility weights and gamma distributions for costs, and sampled over 2000 iterations for each variable of interest.

Model outcomes

The model outcomes included the average and incremental costs and benefits of CRC screening, measured in life years and QALYs, an estimate of the number of deaths averted, the relative risk of mortality reduction and the incremental cost-effectiveness ratio (ICER) of screening compared with no-screening in all three subpopulations. ICERs are calculated according the following formula:

$$CER = \frac{cost\ new - cost\ comparator}{effectiveness\ new - effectiveness\ comparator}.$$

Ethics

Ethics approval for this study was not required as no patients directly participated. Clinical parameter estimates for the model were sourced from published literature and from de-identified data from existing data registry.

RESULTS

Base-case analysis

In the base-case analysis, we assumed that the screening participation rate was 70% (but varied between a conservative estimate of 40–80% in the sensitivity analysis), and the starting age for screening was at 50 years. Table 1 shows the average, and the incremental costs and benefits of screening CRC among dialysis patients waiting for transplants, dialysis patients not on the transplant waiting list and the kidney transplant populations. A total of 2.62 days of life were saved from screening for CRC compared with no screening in the dialysis patients not on the transplant list. Among those waiting for a deceased donor transplant and those who have already received a kidney transplant, a total of 6.9 and 12.0 days of life, respectively, were saved through screening CRC

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Table 1. Incremental cost-effectiveness ratios CRC screening in the dialysis and transplant populations (screen start age = 50)

Populations	Strategies	Average cost per patient ($)	Incremental cost per patient ($)	Average benefits per patient (LYS)	Incremental benefits per patient (LYS)	Average benefits per patient (QALYs)	Incremental benefits per patient (QALYs)	ICER ($/LYS)	ICER ($/QALY)
Dialysis patients not on waiting list	Screening	396 609	883.0	6.1167	0.00718	5.7033	0.0130	122 976	138 828
	No screening	395 726		6.1236		5.6904			
Listed dialysis patients	Screening	520 531	1619	9.3499	0.0190	6.1507	0.0133	85 095	121 973
	No screening	518 912		9.3308		6.1374			
Transplanted patients	Screening	146 236	834	10.2971	0.0333	8.0457	0.0181	25 036	44 790
	No screening	145 401		10.2638		8.0275			

compared with no screening. Compared with no screening, the ICER for screening CRC in CKD were $138 828 per QALY [$122 977 per life year saved (LYS)] among dialysis patients not on the waiting list, $121 973 per QALY ($ 85 095 per LYS) among patients listed on the transplant waiting list and $44 790 per QALY ($25 076 per LYS) in transplanted patients.

Sensitivity analysis

The model was robust to changes in the following variables over the ranges tested in the sensitivity analysis: test sensitivity, the participation rates of screening and the costs of the screening tool. Figure 2 shows the variability of the ICERs with the influential variables being tested over a range of values in the one-way sensitivity analyses across the three CKD populations. The direction of the arrows indicates the direction in which the variables changed between the lowest and the highest estimates shown on either side of the bar. For example, if the prevalence of disease was varied between 1.25 (base-case) to over 5-fold greater than that of the general population, the ICER for screening (compared with no screening) among the dialysis patients listed for transplantation then reduced from $121 937/QALY gained to less than $85 095/QALY gained. Test specificity (and not test sensitivity) was the most influential variable on the overall cost-effectiveness of screening, and was consistent across the three CKD populations. If the test specificity was varied between 99 and 70%, the ICER then varied between $82 871/QALY to over $260 000/QALY. Other variables that are considered to be influential include the discount rates of costs and benefits, the prevalence of disease, the costs of the screening tool (iFOBT) and the starting age of the screening programme.

Table 2 shows the effects of age and the incremental costs, benefits and the ICER between screening and no screening for CRC among the listed dialysis patients. The apparent improvement in the ICERs comparing screening CRC and no screening is driven predominately by a reduction in the incremental costs rather than an increase in the incremental gains in life years associated with the varying starting ages of screening. Older dialysis patients are more likely to experience premature deaths from cardiovascular disease, resulting in a reduction in the overall costs of maintenance dialysis in both arms and the subsequent screening costs in the screened arm. For example, the incremental costs comparing screening and no screening varied between $1619 and $410, if the starting age of screening was pushed back from 50 to 70 years of age. On the contrary, the incremental gains in quality-adjusted life years varied between 0.013 and 0.0041 QALYs if the starting age for screening was increased from 50 to 70 years.

Probabilistic sensitivity analysis

The scatter plots shown in Figure 3 illustrate the incremental costs and health outcomes, and the uncertainties surrounding the mean cost and effect estimates (represented by the orange circles) associated with screening for CRC and no screening among dialysis patients not listed on the transplant waiting list, patients listed on the waiting list
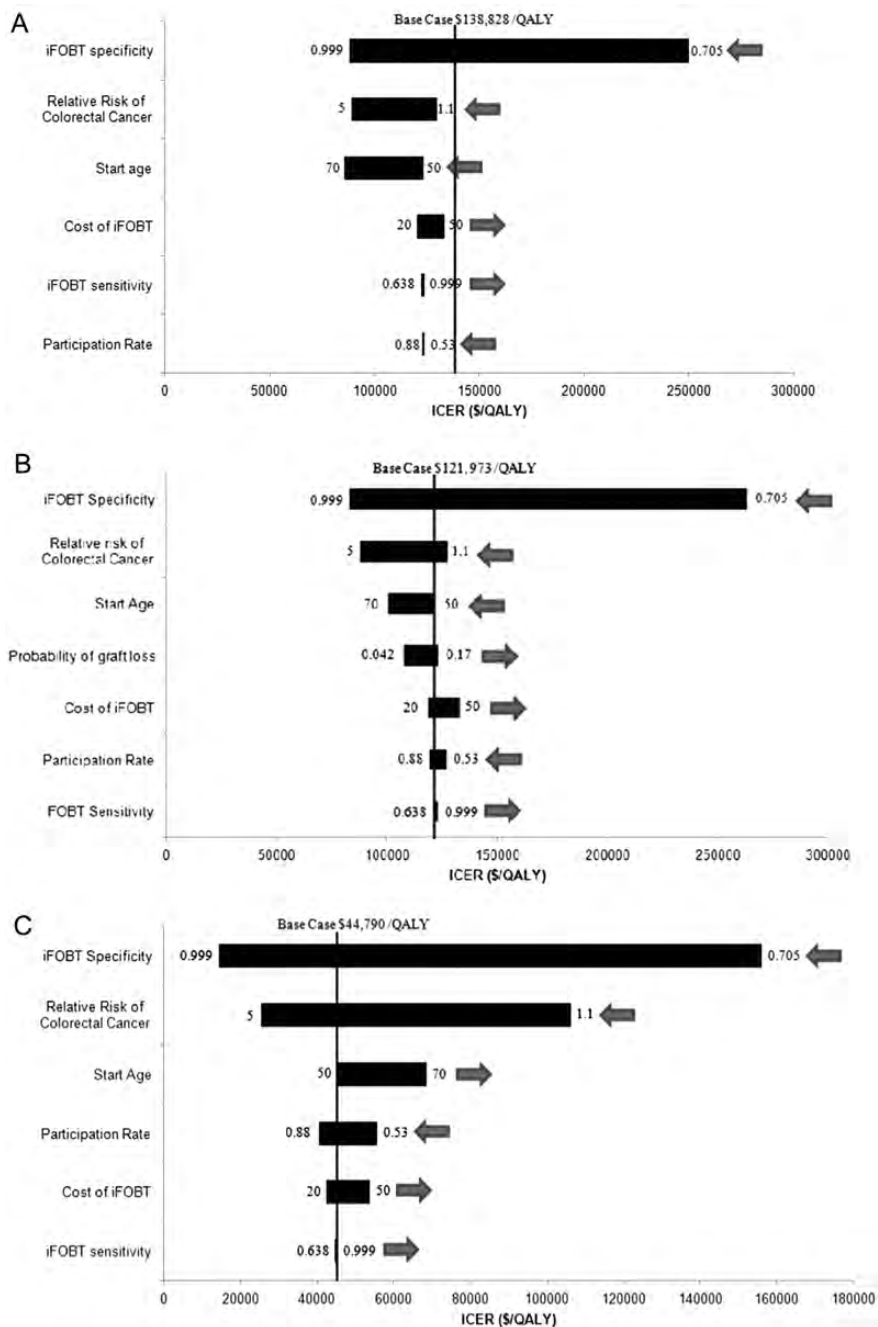
FIGURE 2: One-way sensitivity analyses indicating the potential variation in ICER estimates by altering certain inputted variables for the different subpopulations: (**A**) dialysis patients not on the waiting list, (**B**) listed dialysis and (**C**) transplanted patients.

and the transplanted patients. The *x*-axis represents the incremental gains in QALYs, and the *y*-axis represents the incremental costs of screening over no screening in the three different CKD populations. As would be expected, the cost and effect pairs are located on the northeast (NE) quadrant of the cost-effectiveness plane, with positive incremental costs and effects, indicating that screening is more effective but also more costly than no screening. Compared with no screening, screening for CRC among patients on the transplant waiting list gained on average, a total of 4.9 days of QALYs, whereas screening in the transplanted populations gained on average, a total of 6.9 days of QALYs. For

dialysis patients not on the transplant waiting list, a total of 4.7 days of QALYs were gained through screening compared with no screening.

Figure 4 shows the results of the probabilistic sensitivity analyses in the form of the cost-effectiveness acceptability curve (CEAC). A CEAC shows the probability that an intervention is cost-effective compared with the alternative, given the observed data, for a range of maximum monetary values that a decision-maker might be willing to pay for a particular unit change in outcome [33]. Using our example in Figure 4, the CEAC indicates that there is a 90% likelihood that the cost-effectiveness of screening CRC

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Table 2. The incremental costs, benefits and incremental cost-effectiveness ratios comparing screening CRC and no screening among dialysis patients on the transplant waiting list with the varying starting ages

| Starting ages	Strategies	Average costs ($)	Incremental costs ($)	Average benefits (QALYs)	Incremental benefits (QALYs)	ICER ($/QALY)
50	No screen	518 911	1619	6.1374	0.0133	121 973
	Screen	520 531		6.1507		
55	No screen	514 737	1745	5.7528	0.0151	115 622
	Screen	516 479		5.7679		
60	No screen	515 251	1627	5.3366	0.0133	122 498
	Screen	516 878		5.3499		
65	No screen	508 610	1341	5.0235	0.0108	123 775
	Screen	509 950		5.0434		
70	No screen	498 835	410	4.8217	0.0041	100 855
	Screen	499 245		4.8258		
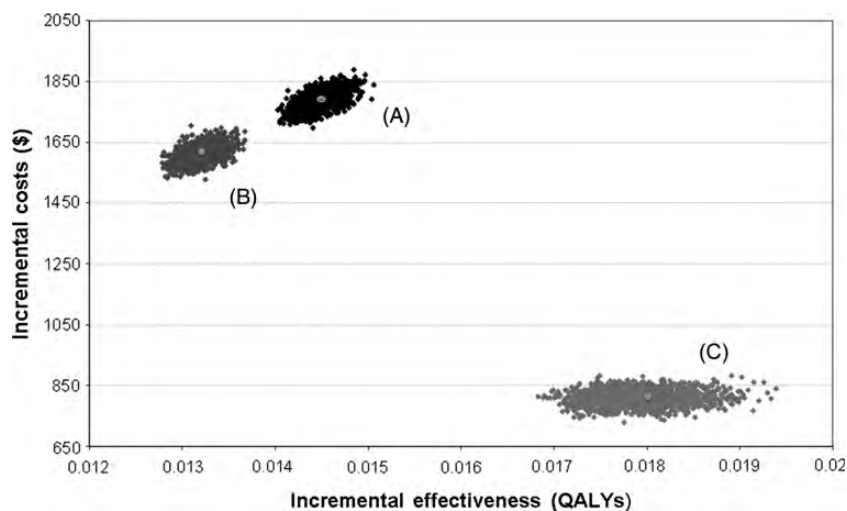
FIGURE 3: Probabilistic sensitivity analysis for (**A**) dialysis patients on waiting list, (**B**) dialysis patients not on waiting list and (**C**) transplanted patients.

using iFOBT compared with no screening in kidney transplant recipients, is less than $60 000 per QALY gained, i.e. given a willingness to pay of $60 000/QALY, the probability that screening CRC is cost-effective is 0.75. On the other hand, if the willingness to pay threshold is $60 000/QALY, screening for CRC in either group of dialysis patients is not cost-effective. Screening for CRC is cost-effective among dialysis patients on the transplant waiting list and not on the transplant waiting list if the willingness to pay threshold is at least $120 000/QALY and $130 000/QALY, respectively.

DISCUSSION

Using the current available evidence from the general and the CKD populations, our modelled analyses suggest that screening for CRC using annual iFOBT saves lives from cancer across the various stages of CKD: dialysis patients not listed on the transplant waiting list, dialysis patients on the waiting list and the transplanted patients. However, the incremental cost-effectiveness thresholds of screening compared with no screening varied considerably between dialysis and
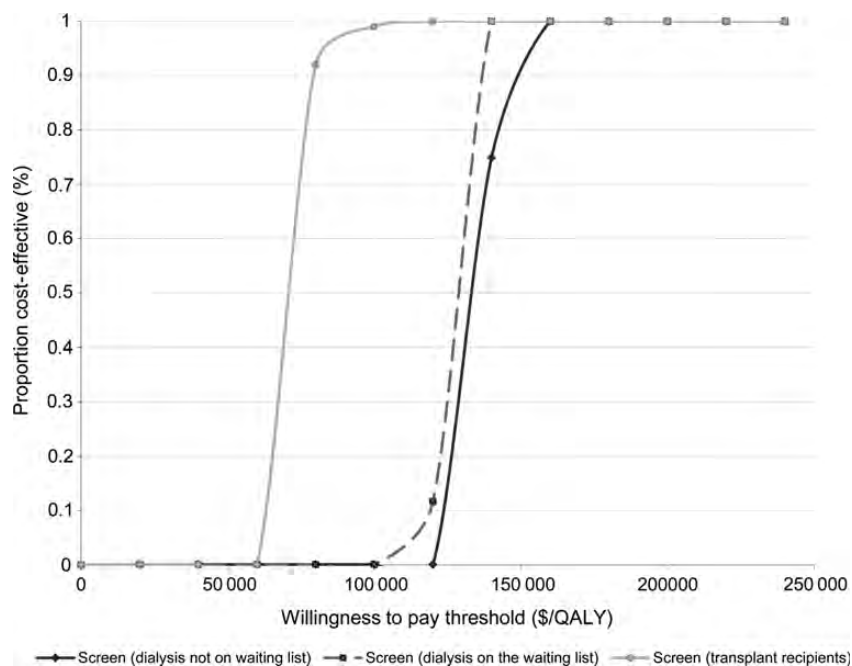
FIGURE 4: Cost effectiveness acceptability curve.

transplanted patients. Assuming screening starts at age 50, the cost-effectiveness of screening CRC varied from $45 000 per QALY gained in kidney transplant recipients to almost $140 000 per QALY gained among patients on dialysis deemed not suitable for transplantation.

The decision to recommend cancer screening in CKD patients is complicated, owing to differences in patient characteristics, patient preferences and also the test properties of the cancer-screening tool in relation to the non-CKD setting. The incremental gains in life years and QALYs due to screening in patients with CKD, particularly among those on dialysis and not listed on the transplant waiting list, are much lower than expected in the general population for a number of reasons. Many people on dialysis will die prematurely from cardiovascular-related events before developing cancer. The benefits gained through screening are driven mainly by a reduction in cancer deaths through treatment of less-advanced screen-detected disease [6, 8, 11, 23], and the absolute risk of dying from competing cardiovascular events among dialysis patients, who are deemed not suitable for transplantation, is at least 5- to 10-fold greater than that of those in the general population [34, 35]. However, for those who have already received a kidney transplant, screening may be worthwhile, largely because of their relatively preserved survival and the heightened risk of cancer owing to on-going immunosuppression. Although our modelled results showed that screening among dialysis patients listed on the transplant waiting list achieved a greater gain in QALYs compared with those not on the list, data of mortality benefits supporting the role of early detection for bowel cancer among dialysis patients whilst waiting for a transplant is lacking and clinical practice guidelines generally do not specify the screening modality and the screening frequency for cancer among those on the transplant waiting list [36].

Besides the differences in life expectancy and prognoses of patients with CKD, the diagnostic accuracies of the screening tool are also likely to be different than in people without CKD. Patients with CKD are more likely to experience gastrointestinal bleeding from dysfunctional platelets secondary to uraemia, use of anti-coagulation during dialysis and anti-platelet agents for primary and secondary cardiovascular risk prevention, which then may affect the overall test specificity of the screening tests [37–39]. We have demonstrated from our decision analytical modelling that test specificity is the most influential variable in the screening algorithm for CRC in CKD. If the test specificity was assumed to be 50%, the overall ICER for screening CRC in the listed dialysis population compared with no screening was over $260 000/QALYs. However, if the false-positive rates are negligible with the test specificity assumed to be >99%, the overall ICER for screening CRC in patients on dialysis waiting for a kidney transplant was reduced to less than $80 000/QALYs. These findings were similar in the transplanted population.

Estimates of the test performance characteristics for CRC screening are well defined in the general population, but there is limited information about the test accuracy of iFOBT screening in the CKD population. A single diagnostic test study evaluating the positive predictive value (PPV) of iFOBT for clinically important colonic lesions in the pre-dialysis population reported a favourable PPV estimate of 30.2%, and the predictive value appeared to increase as the severity of CKD increased. However, a single estimate of test performance such as PPV is insufficient for decision-making. Estimation of other characteristics such as test specificity, sensitivity and negative predictive values were not obtained due to the lack of follow-up to detect interval cancers and advanced neoplasia [40]. A similar study was performed on maintenance dialysis patients using guaiac faecal occult blood tests. The overall positivity rate was at least 20% [41]. Gastritis, arteriovenous

malformations and colonic polyps were the most common lesions on diagnostic gastroscopy and colonoscopy after positive screening tests. Similarly, the lack of adequate follow-up time precluded an accurate estimation of the test performance characteristics of the screening tests [41].

In addition to the physical and psychological harms associated with screening CRC in CKD, including anxiety created from knowledge of positive screen results, over diagnosis is a major issue in CRC screening [42]. In our current model, we assumed that the natural history of CRC in CKD follows the typical adenoma-dysplasia and carcinoma sequence as observed in the general population. Previous observational studies and randomized, controlled trials of screening in the general population suggested that the removal of adenomatous polyps using colonoscopic polypectomies reduces the cumulative incidence of CRC by at least 66% [43, 44]. Among those with CKD, the clinical significances of adenomatous and non-adenomatous lesions are unclear. It is likely that long-term immunosuppressant use may accelerate the progression of pre-malignant adenomatous lesions to cancer, but so far, no published evidence has shown convincing and definitive causative effects of immunosuppressant use and cancer risks of the gastrointestinal tracts. Removing polyps in patients with CKD increases the costs and risks (particularly bleeding) of colonoscopy, potentially without genuine clinical benefit. Instead of affecting cancer mortality, such interventions may only benefit an intermediate outcome which does not have the same prognostic significance, particularly in patients with co-existing co-morbidities and reduced expected life expectancies.

Our study has several strengths. To our knowledge, this is the first modelled analysis, using prospectively collected utility-based quality-of-life data from patients with CKD who valued the quality of life of having cancers [28], to assess the direct health care costs and benefits of CRC screening in patients on dialysis and with kidney transplants. Using probabilistic sensitivity analyses, we have taken into consideration the joint uncertainties surrounding the distribution of individual parameter estimates. Our study does have some potential limitations. First, in the absence of trial-based data in the CKD population, the test performance characteristics of the screening tool, the stage distribution of disease and the cancer-specific mortality risks in the screened and unscreened arms were sourced from the general population. Therefore, estimates used in the current model may over-estimate the benefits experienced by our patients, especially those with more severe co-morbid diseases. Given the lack of cancer-specific mortality data among the dialysis patients not on the transplant waiting list, we have extrapolated mortality information from all dialysis patients. We may have overestimated the gains in life expectancy associated with screening among the dialysis populations deemed not suitable on the waiting list. We have also not taken into consideration patient preferences and perspectives in our modelling. Understanding patients' preferences in shared-decision making for intervention such as cancer screening is particularly relevant for our CKD population. In the absence of trial-based evidence of harms and benefits of early detection for cancer in CKD,

patients' preferences for the outcomes of treatment are central to determining the optimal screening strategies. Recently published surveys and reviews reported that CKD patients may be aware of the heightened risk of cancer after transplantation and on dialysis, but early detection of the disease through screening is not a major health priority because of their pre-occupation with other more imminent issues such as their graft function [45, 46]. Finally, we had not allowed co-morbidities such as cardiovascular and diabetes with cancer in the model, which may potentially affect the overall mortality benefits through screening in the dialysis and transplant populations.

CONCLUSIONS

Although screening using iFOBT in kidney transplant patients and those on dialysis appeared to save lives from cancers, the benefits, harms and costs of screening in patients with CKD are subject to variability of the test specificity of screening iFOBT, life expectancy of the patients, patients' preferences for screening and the prevalence of cancer in CKD. Future studies should be conducted to address these major evidence gaps to ensure screening CRC is effective, efficient and safe in patients with CKD.

AUTHORS' CONTRIBUTION

GW designed and performed the research, analysed the data analysis and wrote the manuscript. ML designed and performed the research, analysed the data, and contributed to the writing of the paper. KH advised on performance of the research and data analysis and contributed to writing of paper. DH designed and performed the research and also analysed data. JRC advised on the performance of the research and revised the manuscript. MB advised on the performance of the research and revised the manuscript. RT advised on the statistical analyses of the research and revised the manuscript. AT advised on the performance of the research and revised the manuscript. JCC participated in data analysis and writing of the paper.

CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Kiberd. Colorectal cancer screening in kidney disease patients: working Backwards. *Nephrol Dial Transplant* 2013; 28: 774–777.)

REFERENCES

1. National Cancer Institute. Surveillance Epidemiology and End Results Stat Fact Sheets: Colon and Rectum Cancer. http://seer.cancer.gov/statfacts/html/colorect.html

2. Australian Government Australian Institute of Health and Welfare (AIHW). Cancer Incidence Data Cubes. 2005; http://www.aihw.gov.au/cancer/data/datacubes/index.cfm (6 December 2010, date last accessed)

3. O'Leary BA, Olynyk JK, Neville AM et al. Cost-effectiveness of colorectal cancer screening: comparison of community-based flexible sigmoidoscopy with fecal occult blood testing and colonoscopy. J Gastroenterol Hepatol 2004; 19: 38–47

4. Launoy GD, Bertrand HJ, Berchi C et al. Evaluation of an immunochemical fecal occult blood test with automated reading in screening for colorectal cancer in a general average-risk population. Int J Cancer 2005; 115: 493–496

5. Zhu MM, Xu XT, Nie F et al. Comparison of immunochemical and guaiac-based fecal occult blood test in screening and surveillance for advanced colorectal neoplasms: a meta-analysis. J Dig Dis 2010; 11: 148–160

6. Hardcastle JD, Chamberlain JO, Robinson MHE et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996; 348: 1472–1477

7. Hewitson P, Glasziou P, Watson E et al. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (Hemoccult): an update. Am J Gastroenterol 2008; 103: 1541–1549

8. Kronborg O, Fenger C, Olsen J et al. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet 1996; 348: 1467–1471

9. Mandel JS, Bond JH, Church TR et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. N Engl J Med 1993; 328: 1365–1371

10. Quintero E, Castells A, Bujanda L et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012; 366: 697–706

11. Lindholm E, Brevinge H, Haglind E. Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer. Br J Surg 2008; 95: 1029–1036

12. Almog R. The public prefers fecal occult blood test over colonoscopy for colorectal cancer screening. Eur J Cancer Prev 2008; 17: 430–437

13. Hawley ST, Volk RJ, Krishnamurthy P et al. Preferences for colorectal cancer screening among racially/ethnically diverse primary care patients. Med Care 2008; 46: S10–S6 doi: 10.1097/MLR.0b013e31817d932e.

14. Saeed F, Agrawal N, Greenberg E et al. Lower gastrointestinal bleeding in chronic hemodialysis patients. Int J Nephrol 2011;2011:Article ID 272535, 8 pages, doi:10.4061/2011/272535

15. Zuckerman GR, Cornette GL, Clouse RE et al. Upper gastrointestinal bleeding in patients with chronic renal failure. Ann Int Med 1985; 102: 588–592

16. Hiremath S, Holden RM, Fergusson D et al. Antiplatelet medications in hemodialysis patients: a systematic review of bleeding rates. Clin J Am Soc Nephrol 2009; 4: 1347–1355

17. Heher EC, Thier SO, Rennke H et al. Adverse renal and metabolic effects associated with oral sodium phosphate bowel preparation. Clin J Am Soc Nephrol 2008; 3: 1494–1503

18. Wechsler A, Schneider R, Sapojnikov M et al. Bowel cleansing in patients with chronic renal failure—an often overlooked hazard. Nephrol Dial Transplant 2006; 21: 1133–1134

19. Wong G, Howard K, Craig JC et al. Cost-effectiveness of colorectal cancer screening in renal transplant recipients. Transplantation 2008; 85: 532–541

20. Kiberd BA. Screening for prostate, breast and colorectal cancer in renal transplant recipients. Am J Transplant 2003; 5: 619–625

21. Australian and New Zealand Dialysis and Transplant Registry. The 33rd Annual Report. Adelaide: ANZDATA Registry, 2010

22. Vajdic CM, McDonald SP, McCredie MRE et al. Cancer incidence before and after kidney transplantation. JAMA 2006; 296: 2823–2831

23. Mandel JS, Church TR, Ederer F et al. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. J Natl Cancer Inst 1999; 91: 434–437

24. O'Connell JB, Maggard MA, Ko CY. Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. J Natl Cancer Inst 2004; 96: 1420–1425

25. Gunderson LL, Sosin H, Levitt S. Extrapelvic colon—areas of failure in a reoperation series: Implications for adjuvant therapy. Int J Radiat Oncol Biol Phys 1985; 11: 731–741

26. Lee YTM. Local and regional recurrence of carcinoma of the colon and rectum: I. Tumour-host factors and adjuvant therapy. Surg Oncol 1995; 4: 283–293

27. Sargent DJ, Wieand HS, Haller DG et al. Disease-free survival versus overall survival as a primary end point for adjuvant colon cancer studies: individual patient data from 20 898 patients on 18 randomized trials. J Clin Oncol 2005; 23: 8664–8670

28. Wong G, Howard K, Chapman J et al. How do people with chronic kidney disease value cancer-related quality of life? Nephrology 2012; 17: 32–41

29. Australian Government National Health and Medical Research Council. Clinical Practice Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer, 2005 [3]; 32–45. http://www.nhmrc.gov.au/guidelines/publications/cp106

30. Australian Government Australian Institute of Health and Welfare (AIHW). Australian Refined Diagnosis Related Groups Data Cubes from 1998–99 to 2007–08, Version 5.0/ 5.1. http://www.aihw.gov.au/hospitals/datacubes/datacube_ardrg.cfm (6 December 2010, date last accessed)

31. Australian Government Department of Health and Ageing. Medicare Benefits Schedule Book. Canberra ACT: AIHW, 2006.

32. Cancer Institute NSW. eviQ Cancer Treatments Online – Colorectal Chemotherapy Protocols. https://www.eviq.org.au/Category/tabid/65/categoryid/328/Default.aspx (20 December 2010, date last accessed)

33. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Econ 2001; 10: 779–787

34. Anavekar NS, Pfeffer MA. Cardiovascular risk in chronic kidney disease. Kidney Int 2004; 66(Suppl 92): S11–S15

35. Foley RN, Parfrey PS, Samak MJ. Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol 1998; 9 (12 Suppl): S16–S23

36. Batabyal. ea. Clinical practice guidelines on waitlisting for kidney transplantation: consistent and equitable? Transplantation 2012; 94: 703–713

37. Sawhney MS, McDougall H, Nelson DB et al. Fecal occult blood test in patients on low-dose aspirin, warfarin, clopidogrel, or

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non-steroidal anti-inflammatory drugs. Dig Dis Sci 2010; 55: 1637–1642

38. Levi Z, Rozen P, Hazazi R et al. Sensitivity, but not specificity, of a quantitative immunochemical fecal occult blood test for neoplasia is slightly increased by the use of low-dose aspirin, NSAIDs, and anticoagulants. Am J Gastroenterol 2009; 104: 933–938

39. Brenner H, Tao S, Haug U. Low-dose aspirin use and performance of immunochemical fecal occult blood tests. JAMA 2010; 304: 2513–2520

40. Bini EJ, Kinkhabwala A, Goldfarb DS. Predictive value of a positive fecal occult blood test increases as the severity of CKD worsens. Am J Kidney Dis 2006; 48: 580–586

41. Akmal M. The prevalence and significance of occult blood loss in patients with predialysis advanced chronic renal failure (CRF), or receiving dialytic therapy. Clin Nephrol 1994; 42: 198–202

42. Robinson MHE, Hardcastle JD, Moss SM et al. The risks of screening: data from the Nottingham randomised controlled trial of faecal occult blood screening for colorectal cancer. Gut 1999; 45: 588–592

43. Winawer SJ, Zauber AG, Ho MN et al. Prevention of colorectal cancer by colonoscopic polypectomy. N Engl J Med 1993; 329: 1977–1981

44. Quintero E. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012; 366: 697–706

45. Williams NC, Tong A, Howard K et al. Knowledge, beliefs and attitudes of kidney transplant recipients regarding their risk of cancer. Nephrology 2012; 17: 300–306

46. Howell M, Tong A, Wong G et al. Important outcomes for kidney transplant recipients: a nominal group and qualitative study. Am J Kidney Dis 2012; 60: 186–196

47. Australian Government Australian Institute of Health and Welfare (AIHW). National Bowel Cancer Screening Program: annual monitoring report 2009 data supplement 2010. 2010 http://www.aihw.gov.au/publications/index.cfm/title/12136 (14 December 2010, date last accessed)

48. Bauer FW, Robbins SL. An autopsy study of cancer patients. JAMA 1972; 221: 1471–1474

49. Burton EC, Troxclair DA, Newman WP. Autopsy diagnoses of malignant neoplasms. JAMA 1998; 280: 1245–1248

50. Papaconstantinou HT, Sklow B, Hanaway MJ et al. Characteristics and survival patterns of solid organ transplant patients developing & lt;i& gt;De Novo& lt;/i& gt; colon and rectal cancer. Dis Colon Rectum 2004; 47: 1898–1903

51. Buell JF, Papaconstantinou HT, Skalow B et al. De novo colorectal cancer: five-year survival is markedly lower in transplant recipients compared with the general population. Transplant Proc 2005; 37: 960–961

52. Lüning T, Keemers-Gels M, Barendregt W et al. Colonoscopic perforations: a review of 30 366 patients. Surg Endosc 2007; 21: 994–997

53. Mai C-M, Wen C-C, Wen S-H et al. Iatrogenic colonic perforation by colonoscopy: a fatal complication for patients with a high anesthetic risk. Int J Colorectal Dis 2010; 25: 449–454

54. Jansman FGA, Postma MJ, van Hartskamp D et al. Cost–benefit analysis of capecitabine versus 5-fluorouracil/leucovorin in the treatment of colorectal cancer in the Netherlands. Clin Ther 2004; 26: 579–589

55. Cass A, Chadban S, Craig J et al. The Economic Impact of End-Stage Kidney Disease in Australia. Sydney: The George Institute, 2006

G. Wong et al.