

# Colorectal Cancer after Kidney Transplantation: Risks and Implications for Screening and Early Detection

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## Abstract

**Colorectal cancer is the third most common solid organ cancer after lung and urinary tract cancers in the kidney transplant population, with at least a twofold excess risk compared to the age- and gender-matched general population. The pattern of increased risk appears to be greatest among younger recipients, with a relative increased risk of at least 20-times in patients aged less than 35 years, compared to a 1.5-fold increased risk among those older than 50 years. Kidney transplant recipients diagnosed with colorectal cancer have a worse prognosis than patients without transplants. The overall five-year survival rate of colorectal cancer is less than 20%. Cancers are often found at a much later stage, with more aggressive and worse oncologic outcomes than cancers in the general population. Cancer screening, which allows early detection of disease, is effective in reducing cancer-specific mortality in the general population. In the transplant population, the ratio of benefit to harm from screening is less well-defined and is likely to be different compared to the general population. Using colorectal cancer as an example, this review addresses the unknowns of early cancer detection, including the test performance characteristics of the screening tools, the treatment benefits of identifying early stage disease, the cost-benefits of screening compared with no screening, and patient preferences for the different screening strategies among kidney transplant recipients. (Trends in Transplant. 2011;5:144-52)**

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## Key words

**Kidney transplantation. Colorectal cancer. Cancer screening.**

## Introduction

Cancer is a major cause of mortality and morbidity following kidney transplantation.

After cardiovascular disease, cancer is the second major cause of death among recipients of kidney transplants. There is now established evidence from registry data and observational studies showing a 2.5- to 3-fold increase in the overall cancer risk among kidney transplant recipients<sup>1-3</sup>. Moreover, the risk increases exponentially with viral-related neoplasms such as human papilloma virus-related urogenital cancers, human herpesvirus 8-associated Kaposi's sarcoma, and Epstein-Barr virus-related posttransplant lymphoproliferative

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disease, with an excess risk at least 5-30 times greater than in the age- and gender-matched general population<sup>4</sup>. In addition, the excess risk of cancer among transplant recipients is inversely related to age. The greatest relative increased risk of cancer was experienced by recipients aged less than 25 years, with the overall risk declining towards that of the general population with increasing age<sup>5</sup>.

Survival among recipients with advanced-stage cancer is poor. The overall five-year survival for all cancers after initial diagnosis in the Australian and New Zealand kidney transplant cohort is less than 10%<sup>6</sup>. In a recent population-based study in Spain, the majority of cancer was diagnosed at advanced stage, with less than 50% of transplanted patients with cancer surviving the first year after cancer diagnosis. The average survival time from tumor diagnosis is 9.6 months<sup>7</sup>. In the USA, a greater relative and cumulative risk of cancer deaths, by at least 5- to 26-fold, was observed in younger transplanted patients with cancer compared to the age- and gender-matched population with cancer<sup>8,9</sup>.

### **Prevention, Screening and Treatment for Cancer in Kidney Transplant Recipients**

Despite the increased risk and poor cancer prognoses, strategies to improve cancer outcomes are limited in kidney transplant recipients. There is emerging data showing that altering the intensity and type of immunosuppression, such as switching to mammalian target of rapamycin (mTOR) inhibitors, may be of benefit for patients who are at higher risk for certain cancer types such as renal cell carcinoma and skin cancers<sup>10-17</sup>. However, there is sparse evidence from observational and trial-based data to suggest cancer-specific mortality benefits with the use of mTOR inhibitors in the kidney transplant population. Converting to mTOR inhibitors for older people

who have a higher absolute risk for cancer may also pose concern. On average, 20% of patients undergoing conversion of mTOR inhibitors experienced significant side effects and are intolerant of the change at the pre-defined therapeutic level, and this is particularly relevant for the elderly who are more prone to experience side effects such as leg swelling, mouth ulcers, hyperlipidemia, and marrow suppression<sup>18</sup>.

The treatment effectiveness of chemotherapeutic agents in transplant recipients may be different after cancer diagnosis. Standard chemotherapy used for cancer treatment can affect the glomeruli, the tubules, and the renal vasculature, in particular for patients with underlying renal impairment, causing kidney dysfunction and acute kidney injury<sup>19</sup>. Minimizing renal toxicity by reducing the recommended dose of chemotherapeutic agents may impede optimal cancer treatment and affect overall treatment outcomes. The use of adjuvant and novel agents for advanced-stage cancer, such as immunotherapy, which activates the patient's immune system, may not be suitable for kidney transplant recipients because of the fear of graft rejection and subsequent allograft dysfunction and failure.

Screening, which detects asymptomatic disease at the preclinical stage, saves lives from cancer in the general population. The potential mortality benefits from screening are mediated by the detection of disease at an earlier stage, thereby allowing effective curative treatment. Screening, however, is not at all benign. Identification of trivial or clinically insignificant disease may lead to overwhelming anxiety, unnecessary diagnostic procedures, and treatment of clinically irrelevant disease. To justify a cancer screening program at a population level, careful consideration of the overall benefits of screening must be balanced against the potential harms. Using colorectal cancer as an example,

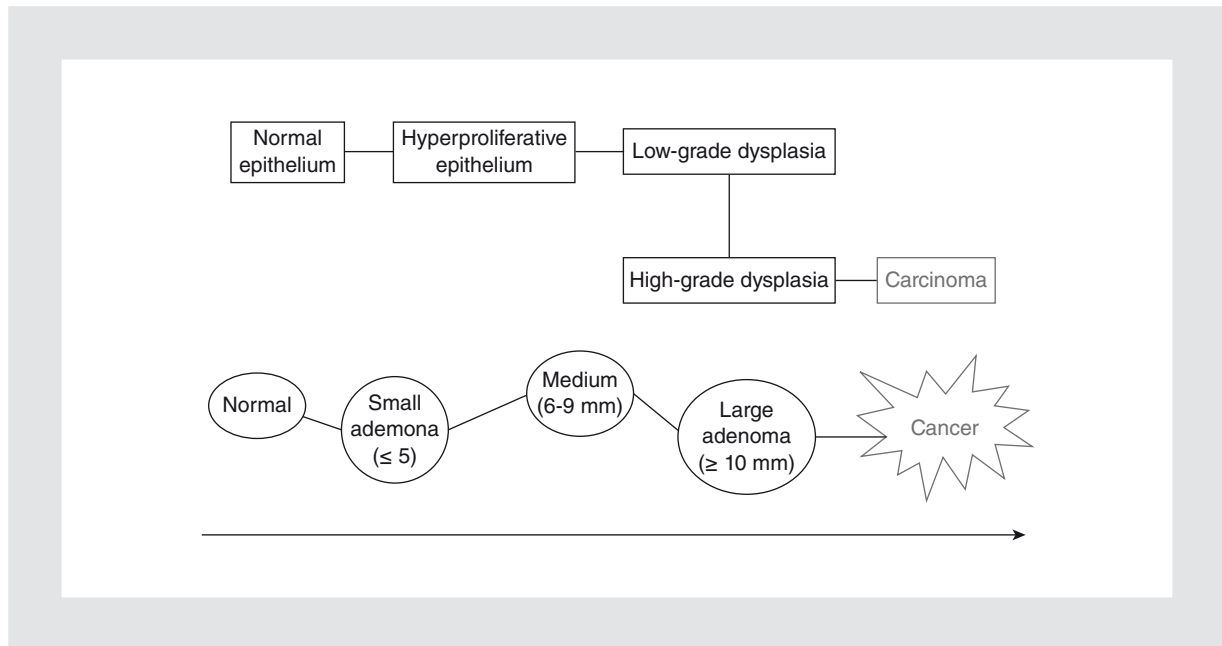


Figure 1. The natural history of colorectal cancer.

we will examine and discuss how cancer screening may be different in the kidney transplant population, and routine screening using the standard recommended tools and strategies may not be applicable to all kidney transplant recipients.

## Colorectal Cancer in the General Population

Colorectal cancer is the second most common cancer in the general population and is the second leading cause of cancer death in the general population. The lifetime risk of colorectal cancer is 1/17 for men and 1/26 for women. On average, colorectal cancer costs over AUS\$235 million to the Australian government and over US\$1 billion in direct health-care costs in the USA annually<sup>20,21</sup>.

Colorectal cancer is largely asymptomatic at a treatable early stage, with an average five-year cancer-specific survival of over 90% if the cancer is limited to the mucosa of the lower intestinal tract. The average cancer

survival reduces to less than 5% if distant metastases are found at initial diagnosis. Over 90% of cancers found in the colon and the rectum are adenocarcinomas, arising from the benign growth of adenomatous polyps. Other types of polypoid structures, such as the inflammatory and hyperplastic polyps, are considered to have no malignant potential. Advanced neoplasia, defined as an adenoma with a diameter  $\geq 10$  mm, a villous or villotubular type, is more likely to progress to cancer than other tumor types<sup>22-24</sup>. Figure 1 shows the natural history of colorectal cancer progression in the general population.

Several risk factors have been associated with advanced colonic neoplasms in the general population, including: age, a family history of colorectal cancer, current consumption of moderate to heavy amounts of alcohol, current smoking, obesity, and high dietary fat intake. Other factors that may be associated with an inverse relationship include: the use of nonsteroidal anti-inflammatory drugs, and higher levels of dietary consumption of cereal fiber, vitamin B, and vitamin D<sup>25,26</sup>.

The management of colorectal cancer in the general population is stage-specific. For early stage disease, treatment is curative with surgical intervention. Among those with more advanced-stage disease but without systemic spread, such as patients with Duke C or high-risk Duke B colon cancer, adjuvant chemotherapy with 5FU (folinic acid) and levamisole is recommended<sup>27</sup>. Other novel treatments, such as immunotherapy and monoclonal antibody therapy, have been considered, but no definitive treatment benefits for overall survival and failure-free survival were observed in recently published trials<sup>28-31</sup>.

### **Colorectal Cancer in the Kidney Transplant Population**

Colorectal cancer is the third most common solid organ cancer in kidney transplant recipients. The overall risk of colorectal cancer is increased by at least 2- to 2.5-fold in the kidney transplant population and the pattern of increased risk appears to be the greatest among the younger patients. The standard incidence ratio (SIR) for younger patients is 13.5, falling to < 3 among older patients aged 55 and older when compared to the age- and gender-matched general population<sup>5</sup>. Table 1 shows the standard incidence ratios of colorectal cancers among kidney transplant recipients in five different countries. Not only is the risk of colorectal cancer higher among kidney transplant recipients compared to the general population, but also cancer prognoses are worse. Cancers are often found at a much later stage with more aggressive and worse oncologic outcomes than cancers in the general population. In the Australian and New Zealand kidney transplant cohort, the relative risk of death from colorectal cancer is increased by at least 2.5- to 3-fold, compared to those with colorectal cancer but without kidney transplants, with an overall five-year survival rate of less than 20%<sup>32</sup>. In a recent

**Table 1. Standardized incidence ratio of colorectal cancer in kidney transplant recipients\***

	<b>SIR (95% CI)</b>
USA <sup>1</sup>	1.5 (1.1-1.9)
Australia and New Zealand <sup>4,5</sup>	2.5 ( 2.4-2.6)
Finland <sup>3</sup>	3.9 (2.1 -6.7)
Korea <sup>34</sup>	2.9 (2.8 -3.1)

\*Standardized incidence ratio (SIR) is the ratio of the observed number of cancers in the kidney transplantation population compared to the expected number of cancers in the general population adjusted for the effects of age and gender.

case-control study performed by Kim, et al., the two-year survival rate of stages III-IV colorectal cancer among kidney transplant recipients was 41% compared to 75% in the general population, with no patients surviving for more than five years after initial treatment. Transplant recipients were also less likely to receive adequate adjuvant chemotherapy for more advanced-stage cancer than patients without kidney transplants. Less than 50% of recipients with kidney transplants with stage III-IV colorectal cancers received the standard chemotherapeutic treatment compared to over 80% in the general population. Moreover, there was a much higher reported recurrence rate in transplant patients compared to those without kidney transplants (35 vs. 15%), with the majority of cancers recurring systemically within 2.5 years after cancer diagnosis<sup>33</sup>.

The enhanced risk of cancer progression and tumor aggressiveness is unclear, but may be attributed to the tumorigenesis effects of long-term immunosuppression. Others have suggested a potential link between viral infection, such as Epstein-Barr virus and cytomegalovirus, and colorectal cancer in immunocompromised patients. However, there is insufficient high-quality evidence to suggest a causal relationship between viral infections and colorectal cancer in either the general or transplant populations<sup>34</sup>.

## Population Screening for Colorectal Cancer in the General Population

Population screening for colorectal cancer is now established and applied in the general population worldwide. The benefits of routine screening using fecal occult blood testing (FOBT) for men and women aged 50 and above have been established in at least five large-scale, population-based, randomized controlled trials and two recently updated systematic reviews<sup>35</sup>. Screening for colorectal cancer using FOBT is also cost-effective, safe, and is generally acceptable by the general population. The newer immunochemical FOBT, which does not require dietary modification and is unlikely to be affected by medications such as aspirin and iron supplements, is an accurate tool with an estimated test sensitivity of 75-90% and test specificity of 90-95%<sup>35,36</sup>.

Although FOBT is the most commonly used screening modality in the general population, results from a recently published multicentre randomized controlled trial of colorectal cancer screening in the UK for people aged 55-64 years, which compared once-only screening using flexible sigmoidoscopy with no screening, reported a 31% cancer-specific mortality reduction in the distal colon<sup>37</sup>. Similar to the UK study, results from the NORC-CAP trial reported a non-significant reduction in colorectal cancer-specific mortality in the screened group compared with the control group seven years after initial screening. Longer-term results of definitive benefits from the Norwegian study are pending, but favorable outcomes are expected in the 15-year follow-up study<sup>38</sup>.

In Australia, population screening using FOBT was first offered to people aged 50, 55, and 65 years as part of the initial rollout of the National Bowel Cancer Screening Program in 2006<sup>39</sup>. In the UK, the National Health Service (NHS) Bowel Cancer Screening program was established in 2006 for men and

**Table 2. Recommendations for colorectal cancer screening in renal transplant population**

Australia <sup>51-54</sup>	Annual or biennial FOBT at age $\geq 50$ or combination of FOBT + flexible sigmoidoscopy at age $\geq 50$
USA <sup>55</sup>	Annual FOBT and/or sigmoidoscopy every 5 years
Europe <sup>50</sup>	FOBT for recipients aged 50-74
Canada <sup>42</sup>	Annual or biennial FOBT at age $\geq 50$ or combination of FOBT and flexible sigmoidoscopy
Asia <sup>56</sup>	Annual FOBT and/or 5-yearly flexible sigmoidoscopy

FOBT: fecal occult blood test.

women aged 55-64 years using immunochemical FOBT screening<sup>40</sup>. Recent initiatives have prompted extension of the program to those aged 70-74 years. Other countries such as Canada, Spain, and The Netherlands do not have established strategies for population screening, but several pilot studies are now underway to assess the feasibility and practicality of implementing a large-scale, population-based screening program.

## Screening Colorectal Cancer in the Kidney Transplant Population

The evidence that clinicians need to justify population screening for early cancer diagnoses goes beyond knowing that screening saves lives, but also requires evidence of good test accuracy, cost-effectiveness, patient acceptance, and more importantly, hard evidence to show that patients are better off (in terms of overall survival and better quality of life) in the long term when early cancer diagnosis is achieved. Table 2 shows the various current recommendations for colorectal cancer screening in the kidney transplant population. In general, screening guidelines for colorectal cancers are largely extrapolated from that of the general population<sup>41</sup>, but routine cancer

screening among kidney transplant recipients is likely to be different for the following reasons.

### ***Competing Risk of Deaths in Recipients with Coexisting Comorbidities***

Although the absolute and relative risk of colorectal cancer is increased in kidney transplant recipients, routine screening and early detection of disease may not necessarily incur any extra survival benefits in this population. Benefits from cancer screening are driven predominately by the reduction of cancer deaths and not the actual increased detection of disease. Therefore, consideration for routine screening should also take into account the competing risks of death such as the competing cardiovascular events/deaths in patients with kidney transplants. It is likely that recipients with comorbidities, such as diabetes and vascular disease, will die from cardiovascular-related deaths before the likelihood of developing cancer. Some have argued that this may not necessarily be of significant concern because the lead time of cancer development from adenomatous polyps under the influence of immunosuppression is likely to be shorter in transplant recipients than in those without immunosuppression. However, in the absence of epidemiological data on the natural history of disease after transplantation and trial-based data about mortality benefits from screening in kidney transplant recipients, recommendation for mandatory routine screening is premature.

Previous economic-modeled analyses of colorectal cancer screening have reported reduced survival benefits from screening, with the total days of lives saved being one-third to one-half less than the average increase in survival predicted in the general population undergoing the same screening program<sup>42</sup>. In a more recently developed predictive model of screening, screening colorectal in kidney

transplant recipients is cost-effective, reporting a gain of an average 24 days of life compared to no screening over a screening period of 20 years. However, the overall survival benefits and the incremental cost-effectiveness ratios are strongly influenced by the test performance characteristics of the screening tool<sup>43</sup>.

### ***Test Performance Characteristics of the Screening Tool may be Different in Transplant Recipients***

Immunochemical FOBT is the established and recommended screening tool for colorectal cancer in the general population, with an estimated average test sensitivity and specificity over 75 and 95%, respectively. Whilst it would be unrealistic to find a screening test with perfect test sensitivity and specificity, a screening test should have reasonable test sensitivity and an acceptable test specificity to minimize false-negative and false-positive results. In recipients with kidney transplant, the test performance of immunochemical FOBT is likely to be different because of spectrum bias. Spectrum bias refers to the situation whereby the performance characteristic of a diagnostic/screening test changes because of the differences in patient characteristics and case-mix within the different populations, therefore affecting the transferability and generalizability of the test to other settings. Previous studies have shown that anti-platelet use, which is highly prevalent in the transplant population for primary and secondary cardiovascular prevention, can potentially improve the test sensitivity by increasing the propensity of bleeding from existing malignant and premalignant tumors<sup>44</sup>. On the contrary, the use of anti-platelets and immunosuppression, such as mycophenolic acid, can increase the risk of minute gastrointestinal bleeding from sources other than cancers and advanced neoplasms, leading to more false-positive results and reducing the overall specificity of the test.

### ***Treatment Effectiveness of Colorectal Cancer is Likely To Be Different in Transplant Recipients***

Treatment for early stage colorectal cancer is well-established in the general population; for example, the use of endoscopic mucosal resection for high-grade tubular adenoma or surgical resection for localized cancer<sup>45</sup>. In the kidney transplant population, the effectiveness of early cancer intervention is less certain. Cardiovascular disease and other co-existing comorbidities, such as vascular disease, are highly prevalent among individuals with a long-standing history of chronic kidney disease. The feasibility of surgical intervention in this cohort of patients may be limited by their higher underlying anesthetic risk. Transplant recipients are also at higher risk of perioperative complications, such as wound infections, anastomotic leaks and wound dehiscence, because of long-term immunosuppression use. Some of the chemotherapeutic adjuvant agents are nephrotoxic and should ideally be avoided and/or dose-adjusted. Insufficient dosing of the recommended treatment dose may result in undertreatment and ineffective management of early stage disease.

### ***Preferences and Choices for Screening is Unknown Among Kidney Transplant Recipients***

Previous studies have reported substantial variation about the choice that people make regarding colorectal cancer screening in the general population. Although most people preferred some form of screening, the screening choices vary substantially between individuals based upon age, gender, and the inherent properties of the screening tools, such as the test performance characteristics, the complications rate of screening, and subsequent diagnostic procedures, and finally the potential differences in the out-of-pocket costs<sup>46-48</sup>. Screening choices are therefore not

monolithic, and shared decision making should be encouraged between patients and the healthcare providers to ensure an informed and patient-focused screening program.

Despite the greater cancer risks and poorer cancer prognoses among transplant recipients, patient preferences/choices/perspective of cancer prevention and screening are largely unknown. A mixed-method study by Paykin, et al. acknowledged that patients are fairly well informed and knowledgeable about the various aspects of living with transplants, but have limited awareness of their underlying cancer risk, cancer prevention, and screening strategies. Cancer is not an imminent issue and most patients are focused on more immediate concerns, such as graft rejection and infection risk, but tend to disregard the importance and significance of their cancer risk after transplantation<sup>49</sup>. Transplant clinicians should take the initiative of discussing cancer issues, potential cancer warning signs, and the pros/cons of early cancer detection with their patients. Adherence with cancer screening and prevention is associated with one's risk perception, perception of efficacy of the screening tests, and the level of understanding of the effectiveness of screening in early detection of cancer. In-depth understanding about recipients' perception and perspectives about their attitudes and opinions of testing and screening is necessary to allow informed decisions to be made regarding adherence to cancer prevention strategies, uptake of screening, and early detection of cancers, which may lead to improvements in cancer outcomes in this high-risk population.

### **Conclusion**

Cancer screening is a complex issue in kidney transplant recipients. The benefits of early cancer detection may be confounded by coexisting comorbidities, the shorter life

expectancy, and the competing risk of death from causes such as cardiovascular events instead of cancer. Future research is therefore needed to assess the test properties of the proposed screening tools, the cost-benefits-harms ratio of screening against no screening, and to elicit patient preferences for early detection, including information about the screening modalities, the frequency, and the methods of delivery.

## Acknowledgements

Germaine Wong conceived, designed, and wrote the manuscript, Maria Martina contributed to the writing and editing of the manuscript, and Jeremy Chapman conceived, designed, and edited the manuscript.

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