Cancer Screening in Renal Transplant Recipients: What Is the Evidence?

Germaine Wong,**† Jeremy R. Chapman,**‡ and Jonathan C. Craig†

∗National Health and Medical Research Council Centre for Clinical Research Excellence in Renal Medicine, Children’s Hospital at Westmead and ‡Centre for Transplant and Renal Research, Westmead Hospital, Westmead, and †School of Public Health, University of Sydney, Sydney, New South Wales, Australia

Increased cancer risk is well established in the renal transplant population. Little, however, is known about the benefits and harms of cancer screening, treatment effectiveness, and the overall cancer prognosis in renal transplant recipients. In this study, we critically appraised guidelines for cancer screening in the renal transplant and general populations using standard criteria for an evidence-based screening program. Guidelines were included when they were applied to adult participants, had objectives specific to cancer screening, and were written in English. Recommendations for breast and colorectal cancer screening in the general population were supported by evidence of cancer-specific mortality benefits from randomized, controlled trials of cancer screening. Convincing evidence from observational studies had demonstrated population cervical cancer screening was effective, also, test performance of mammography, faecal occult blood testing, and Pap smear were accurate. Population breast, colorectal, and cervical cancer screening also appeared to be good value for money in the general population. On the contrary, recommendations for cancer screening in renal transplant recipients were entirely extrapolated from data in the general population. Studies in the general population have led to the development of cancer screening guidelines in transplant recipients. Because of increased cancer risk, differences in diagnostic test performance, competing risks for deaths from causes such as cardiovascular disease and reduced overall life expectancies, validity of their recommendations are uncertain. Future studies are needed to address these issues to provide the necessary evidence for informed decision-making.

False-positive findings may result in inappropriate and excessive investigations that could be harmful. Guidelines should therefore provide explicit, unbiased, and relevant evidence to inform an individual’s overall risk of disease, benefits, and harms when making the eventual decisions on screening (5).

The aim of this article was to critically appraise practice guidelines on cancer screening in the renal transplant and general populations on the basis of accepted criteria for an evidence-based disease screening program (5–7).

Standard Criteria for an Evidence-Based Screening Program
There are many criteria for assessing screening guidelines and recommendations. In this study, we used the “User’s Guide to the Medical Literature: How to Use Guidelines and Recommendations about Screening” (5). Recommendations should be based on the four recommended criteria: Evidence from randomized, controlled trials (RCT) that earlier intervention is effective; the proposed screening strategies are accurate and cost-effective; and that the extra benefits outweigh the overall harms of the anticipated intervention.

RCT Evidence that Earlier Intervention Is Effective
The benefits attained in screening trials are mediated by shift to a less advanced stage and more effective treatment for earlier diseases. There are two types of screening trial designs. Participants could be randomly assigned to screening and no screening groups. Alternatively, all participants are screened but only those with positive results will be randomly assigned to earlier or standard intervention. In RCT, benefits are defined as significant reduction in cancer-specific mortality and morbidity. Survival benefits, measured from the time of diagnosis, are misleading as a result of length-time and lead-time bias. Individuals only seem to be living longer because indolent diseases, with minimal propensity to progress, are detected earlier, allowing people to live with the disease diagnosed for a longer period of time.

Accuracies of the Screening Tool
It may be reasonable to assume that an accurate screening tool, with optimal test sensitivity and specificity, achieves greater benefits and fewer harms because it detects more true positives at an earlier stage and provides a window of opportunity to commence effective treatment and prevent progression of incurable metastatic disease. This, however, is based on the assumption that such diseases will alter the
individual’s overall survival and quality of life and not remain insignificant during their lifetime. The trade-off for a better, sensitive test is overdetection of inconsequential diseases (8). For example, detecting in a 75-yr-old man low-grade prostate cancer that does not manifest and progress to symptomatic disease during his lifetime will incur unnecessary costs, treatment anxiety, and complications for the individual.

**Cost-Effectiveness of the Intervention**

Given that the demand for health care resources always exceed the supply, cost-effectiveness of any proposed intervention is important to policy makers. Economic evaluations, which present reliable effectiveness estimates while adjusting the costs and trade-offs in the process, have been performed increasingly alongside clinical trials to provide a holistic and comprehensive perspective in clinical decision-making. The quality of the evaluation depends on the quality of the trial; structure and design of the study; accuracy and validity of the collected data; and whether the researcher, using sensitivity analyses, has explored the uncertainty appropriately and explicitly in the parameter estimates. Economic evaluations are critically appraised using these criteria. Failure to address any of these issues will result in invalid assessment.

**Harms and Benefits of Screening**

The benefits of screening must outweigh all harms in any screening decision. If there is clear evidence of benefits from screening trials, then screening may be beneficial only if harms are carefully considered and weighed for each individual. The benefits observed in screening trials may not be generalizable to all participants. The extent of harm varies with uncertainty between individuals. Harms include both the physical and the psychological consequences associated with investigations and treatment of the disease. The choice of screening is therefore an informed decision with clear, unbiased information, provided by guidelines and recommendations, about the risks, benefits, and harms for each individual.

**Results**

Cancer screening guidelines specific to renal transplant recipients from European and American professional bodies were reviewed (9–12). Guidelines from other international societies for the general population were also extracted (13–21). Recommendations made by the two transplantation societies, the American Society of Transplantation (AST) and the European Best Practice Guidelines on renal transplantation (EBPG), were compared with those applied to the general population using accepted criteria for an evidence-based screening program (5,6) (as shown in Tables 2 through 4).

**Breast Cancer Screening**

Most international guidelines suggest screening to commence at age 50 for all women of average cancer risk. Screening intervals recommended by most societies are between 12 and 24 mo (22–24). The ATS and EBPG on renal transplantation recommend breast cancer screening in all female renal transplant recipients between 50 and 69 yr of age. Women between 40 and 49 yr could still undergo screening mammography every 1 or 2 yr, but there is no evidence for or against screening in this age group (11,12).

**Are the Recommendations Valid?** Large randomized, controlled trials in the general population have confirmed that biennial mammographic breast cancer screening reduces breast cancer–related mortality by 20 to 30% (3,4). A stage shift to a more benign phase was also observed, and in most cases, there was a reduction in the incidence of advanced diseases. The sensitivity and specificity of mammography reported were 75 and 94%, respectively (25). In these trials, test accuracies also varied substantially with age and breast density. Sensitivity and specificity were highest in older women with fatty breast tissue and lowest among younger women with denser breast tissue (26).

Recommendations for breast cancer screening in the renal transplant population are based on screening guidelines in the general population. No studies have evaluated the effectiveness and accuracies of mammographic screening in the transplant population. While female transplant recipients have a similar breast cancer risk, before extrapolating from the general populations, consideration must be given to whether they might attain the comparable benefits because of the reduced overall life expectancies, potential differences in test performance, and harms from mammographic breast cancer screening.

**Harms from Breast Cancer Screening.** Potential harms include psychological distress and pain and discomfort with mammographic screening. Complaints from women include machine compression and roughness from the operator (27). Exposure to mammographic x-rays also confers the risk for radiation-induced breast cancer, which is greatest if exposure occurs at a younger age. The risk of benign breast neoplasms has been shown to increase in transplant recipients who have used cyclosporine as part of their immunosuppressive regimen. These adenomas tend to be multiple, large, and dense. An increased incidence of benign breast calcifications was observed in women who had ESKD and were on dialysis, which led to an increased callback rate for biopsies (28). False-positive findings will lead to unnecessary and exhaustive diagnostic procedures such as fine-needle and core biopsies of the breasts (29).

**Cost-Effectiveness of Breast Cancer Screening.** Economic analyses performed using estimates from RCT and population studies have shown that breast cancer screening is relatively cost-effective in the general population. The incremental cost-effectiveness ratio (ICER) ranged between $18,000 and $45,000 per life-year saved (LYS) with biennial mammography (30,31). Models of breast cancer screening in renal transplant recipients suggest that breast cancer screening may be cost-effective in the average-risk nondiabetic white population (32).

**Cervical Cancer Screening**

Cervical cancer screening is recommended in the general population. Most guidelines recommend regular cytologic testing to commence between the ages of 18 and 20 or when sexual activity begins. Some suggest that screening should be deferred until 2 to 3 yr after first sexual intercourse (18,33–35). Waiting 3 yr after first sexual intercourse ensures transient infections that clear spontaneously will not be detected but allows sufficient time to detect cancerous lesions derived from more persistent human papillomavirus (HPV) infection (18,35,36).

Cervical cancer, a virus-related neoplasia, is more aggres-
Table 2. Recommendations for routinely screened cancers in the general population

<table>
<thead>
<tr>
<th>Cancers</th>
<th>Recommendations</th>
<th>RCT Evidence of Screening that Earlier Intervention Works</th>
<th>Test Performance</th>
<th>Cost-Effectiveness, ICER ($/LYS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Trials</td>
<td>Participants (n)</td>
<td>Results</td>
</tr>
<tr>
<td>Breast</td>
<td>Biennial mammography for all women older than 50 yr (23,24)</td>
<td>6 (94)</td>
<td>369,370</td>
<td>Cancer-specific mortality reduction 20 to 24% (94)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Annual or biennial FOBT at age ≥50 (48); combination of FOBT and flexible sigmoidoscopy at age ≥50 (16,17)</td>
<td>4 (96)</td>
<td>329,642</td>
<td>Cancer-specific mortality reduction 15 to 23% (96)</td>
</tr>
<tr>
<td>Cervical</td>
<td>Cytological screening to commence in women age ≥21 yr and/or women within 3 mo of first sexual intercourse (biennially or triennially) (36)</td>
<td></td>
<td></td>
<td>Pap smear, conventional 84.6%; liquid based, 94.2% (44)</td>
</tr>
</tbody>
</table>

FOBT, fecal occult blood testing; ICER, incremental cost-effective ratio; LYS, life-year saved
Table 3. Recommendations for cancers that are not routinely screened in the general population

<table>
<thead>
<tr>
<th>Cancers</th>
<th>Recommendations</th>
<th>RCT Evidence of Screening that Earlier Intervention Works</th>
<th>Test Performances</th>
<th>Cost-Effectiveness, ICER ($/LYS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Trials (n)</td>
<td>Participants (n)</td>
<td>Results</td>
</tr>
<tr>
<td>Prostate</td>
<td>No general consensus</td>
<td>2 (88)</td>
<td>57,511</td>
<td>No significant mortality reduction in the intervention group</td>
</tr>
<tr>
<td></td>
<td>USPSTF found no evidence to recommend for or against routine screening using PSA and DRE (84)</td>
<td></td>
<td></td>
<td>DRE 83.2 (CI 49.0 to 69.2) (88)</td>
</tr>
<tr>
<td></td>
<td>ACS recommends annual screening using PSA and DRE in men older than 50 (18)</td>
<td></td>
<td></td>
<td>Ultrasound 84.3 (78)</td>
</tr>
<tr>
<td></td>
<td>The American College of Physicians made no firm suggestions about screening and believes that the decision to screen should be individualized (85)</td>
<td></td>
<td></td>
<td>Both 60.8 (78)</td>
</tr>
<tr>
<td></td>
<td>Hepatocellular</td>
<td>2 (78)</td>
<td>19,884</td>
<td>No significant mortality reduction in the intervention group</td>
</tr>
<tr>
<td></td>
<td>however, screening using α-fetoprotein testing and abdominal ultrasound should be considered in high risk individuals (13)</td>
<td></td>
<td></td>
<td>Ultrasound 97.1 (78)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Both 95 (78)</td>
</tr>
<tr>
<td>Lung</td>
<td>No recommendation</td>
<td>6 (using CXR and/or sputum exam) (71)</td>
<td>103,441</td>
<td>No significant mortality reduction in the intervention group</td>
</tr>
<tr>
<td>Renal</td>
<td>No recommendation</td>
<td>No RCT to show screening using renal ultrasound improves cancer-specific and overall mortality</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Skin</td>
<td>Insufficient evidence to recommend for or against total body skin examination (64)</td>
<td>1 RCT using total body skin exam is now under way (65)</td>
<td>Total body skin exam 94 (100) (100)</td>
<td>Total body skin exam 98</td>
</tr>
</tbody>
</table>

ACS, American Cancer Society; CXR, chest x-ray; DRE, digital rectal examination; PSA, prostate-specific antigen; RCT, randomized, controlled trial; USPSTF, US Preventive Services Task Force.
sive and develops rapidly in immunocompromised states (37,38). The American College of Obstetrics and Gynaecology specifies that women of high-risk groups should be screened more frequently (36). The two transplantation societies recommend annual cervical cancer screening with Pap smear and pelvic examination in all adult female renal transplant recipients (10,12).

Are the Recommendations Valid? Cervical cancer screening using the Pap test was first introduced in the United States in the early 1950s without evidence of mortality benefits from RCT. Observational studies, based on historical data across the United States and Europe, had demonstrated significant reduction in incidence and mortality of invasive cancer since the introduction of population cytological cancer screening (39).

Some international societies now recommend annual cervical cancer screening with Pap smear and pelvic examination in all adult female renal transplant recipients (10,12).

### Table 4. Recommendations for cancer screening in renal transplant recipients

<table>
<thead>
<tr>
<th>Cancers</th>
<th>Recommendation</th>
<th>RCT Evidence that Earlier Intervention Works</th>
<th>Cost-Effectiveness, ICER ($/LYS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Annual or biennial mammography for all women older than 50 yr</td>
<td>Nil</td>
<td>32,000 (32)</td>
</tr>
<tr>
<td></td>
<td>Women between 40 and 49 could still undergo screening, but no evidence for or against screening at this age (10,12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>Annual FOBT and/or 5-yearly flexible sigmoidoscopy for individuals older than 50 yr (10,12)</td>
<td>Nil</td>
<td>25,189 (32)</td>
</tr>
<tr>
<td>Cervical</td>
<td>Annual cytological cervical cancer screening and pelvic examination once sexually active (10,12)</td>
<td>Nil</td>
<td>No data</td>
</tr>
<tr>
<td>Prostate</td>
<td>Annual DRE and PSA measurement in all male renal transplant recipients older than 50 yr (10,12)</td>
<td>Nil</td>
<td>56,850 (32)</td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>α-Fetoprotein and ultrasound performed every 6 mo in high-risk individuals, but no firm confirmation (10,12)</td>
<td>Nil</td>
<td>No data</td>
</tr>
<tr>
<td>Skin</td>
<td>Monthly self-skin examination, total body skin examination every 6 to 12 mo by expert physicians and dermatologists (11,12)</td>
<td>Nil</td>
<td>No data</td>
</tr>
<tr>
<td>Renal</td>
<td>No firm recommendation; some suggested regular ultrasonography of the native kidneys (10,12)</td>
<td>Nil</td>
<td>No data</td>
</tr>
</tbody>
</table>

HPV DNA testing, however, came at the expense of reduced specificity of the test. This effect is greater on older than younger women. In younger women (<35 yr of age), the overall test specificity of HPV DNA testing reduced to 90% (76.5 to 95.5%) compared with 95.5% with cytological testing. For women ≥35 yr of age, the overall test specificity of HPV DNA testing is 93.3% (87.3 to 96.4%) (40). There is no RCT evidence to confirm its overall mortality and morbidity benefits as a primary screening tool in the general population.

Evidence to support for or against the use of HPV DNA alone or in combination with cytological testing in the renal transplant population is also sparse. Use of immunosuppressive therapy after transplantation may cause reactivation of latent diseases and reduction in host ability to contain HPV infection. There is now emerging evidence to show an increased incidence of oncogenic cervical HPV infections (HPV 16 and 18) among renal transplant recipients (41,42). Uncertainty, however, exists in the likely progression of these oncogenic infections and the significance of detecting early oncogenic
HPV DNA strains in the prevention of future cancers. Early detection and effective eradication of these infections is worthwhile only if there is evidence to show that such practices reduce cancer-related morbidity and mortality.

**Harms from Cervical Cancer Screening.** Screening is a test done on asymptomatic, well women. Screening may identify inconsequential diseases that are not clinically significant. Detection of low-grade diseases and false-positive results can lead to invasive diagnostic procedures, unnecessary treatment, and unwarranted psychological distress. In certain societies and ethnic backgrounds, the diagnosis and labeling of someone with high risk for cervical cancer could create potential prejudice and stigma against the individual; however false-negative results could delay diagnosis and treatment, creating a false sense of security and assurance.

**Cost-Effectiveness of Cervical Cancer Screening.** A number of economic models have evaluated population cervical cancer screening from different countries. Data used in these models originated from historical and observational evidence of cervical screening. Most concluded that cervical cancer screening in the general population is cost-effective. The average ICER ranged between $25,000 and $50,000/LYS with biennial and triennial screening (43,44). The cost-effectiveness of cervical cancer screening among renal transplant recipients has not been assessed.

**Colorectal Cancer Screening**

Most practice guidelines suggested the use of flexible sigmoidoscopy in combination with annual fecal occult blood testing (FOBT) screening every 5 yr in the United States (16–19). In Australia, biennial immunochemical FOBT is the recommended screening tool of the National Health and Medical Research Council of Australia (45). All positive test results must then be followed by total colonic examination using colonoscopy for verification of diagnosis and for treatment if required.

The AST recommends annual FOBT screening and flexible sigmoidoscopy screening every 5 yr to begin in all renal transplant recipients from the age of 50 yr (12). There is no recommendation to begin screening at an earlier age, despite strong evidence to suggest that colorectal cancers occur at a much younger age in transplant recipients (46). The EBPG suggested the use of annual FOBT screening in renal transplant recipients according to the national recommendation in the general population (10).

**Are the Recommendations Valid?** It has been proven by four large RCT that screening for early colorectal cancers and precancerous polyps with guaiac FOBT reduces colorectal cancer mortality (47–50). The test sensitivity varies between 46% (unrehydrated) and 92% (rehydrated) and specificity between 97% (unrehydrated) and 90% (rehydration) (51). The benefits and harms of colorectal cancer screening using flexible sigmoidoscopy are uncertain in both the general and transplant populations. Prospective case-control studies have suggested a cancer-specific mortality reduction of 35% with screening every 3 to 5 yr. These studies, however, were subjected to recall and interviewer biases. Large RCT are now underway in the United States and Europe to assess the benefits of colorectal cancer screening using flexible sigmoidoscopies in the general population (52,53).

Despite having an increased risk and reduced prognosis, no clinical trials to date have evaluated the benefits of colorectal cancer screening in renal transplant recipients. Studies have suggested the positive predictive value (PPV) of FOBT screening in the chronic kidney disease (CKD) population (stages 3 to 5) increases as the severity of CKD increases (54). The impact of renal transplantation on the test performance of FOBT screening, however, is unknown, but there are good reasons to believe that false-positive rates would be increased for a variety of reasons, including increased tendency to bleed as a result of infectious complications, angiodysplasia, direct mucosal drug toxicity, and minor mucosal inflammation (32,55).

**Harms from Colorectal Cancer Screening.** FOBT itself might seem harmless, but the diagnostic colonoscopy that follows carries significant morbidity risks. Potential complications from a colonoscopy include perforations, bleeding, abdominal pain, splenic trauma, subcutaneous emphysema, and problems related to sedation and anesthetic. Patients with CKD and other underlying risk factors for kidney dysfunction, such as diabetes, are also at increased risk for acute phosphate nephropathy after oral phosphate bowel cleansing agents (56–58). Self-testing FOBT is not at all pleasant. It is often untidy and embarrassing for the patient. Patients with false-positive results would have to endure the psychological and physical trauma of exhaustive diagnostic procedures, which seem futile in some cases.

**Cost-Effectiveness of Colorectal Cancer Screening.** Cost-effectiveness and cost-utility analyses have shown that colorectal cancer screening is cost-effective in the general population. In the Australian colorectal cancer screening pilot study, the ICER ranged between A$20,000 and $24,000/LYS with programs targeted at ages between 50 and 74 and between 55 and 74, respectively (59). Using outcomes and costs data from the RCT, the estimated ICER was US $10,000 to $17,000/LYS (60–64). The cost-effectiveness of colorectal cancer screening in renal transplant recipients remains unanswered. Renal transplant recipients confer different disease prevalence, risks, and overall survival, all of which could potentially influence the cost-effectiveness of screening and treatment. Without reliable evidence to confirm the true benefits of FOBT screening in renal transplant recipients, it is inappropriate to implement population colorectal cancer screening in renal transplant recipients. The choice and method of colorectal cancer screening in the average-risk transplant recipient should be assessed on an individual basis.

**Recommendation for Skin Cancer Screening**

The American and European transplantation organizations recommend skin cancer screening in renal transplant individuals using monthly self-skin examination and 6- to 12-monthly total body skin examination by expert physicians and dermatologists. The US Preventive Services Task Force concluded that there is insufficient evidence to recommend for or against population skin cancer screening using total skin examination (64). The American College of Preventive Medicine recommended
that high-risk individuals be screened regularly, but no recommend-
edation was made for individuals with low risk for skin cancers (21).

Are the Recommendations Valid? There is no evidence from RCT to verify that total body skin cancer examination reduces skin cancer mortality and no data to suggest that early treatment for either melanoma and nonmelanocytic skin cancers found by screening reduces the overall skin cancer-related mortality and morbidity in the general and renal transplant populations. An RCT that involves >600,000 participants is now being conducted in Queensland, Australia, to evaluate the mortality and morbidity benefits of skin cancer screening using self-skin and total body skin examination by physician (65). The results of this landmark trial will be available in the next decade.

Harms from Skin Cancer Screening. False-positive results from skin cancer screening can generate anxiety and unnecessary biopsies and procedures in transplant individuals. Risks for poor wound healing, bleeding, and postoperative infections are significantly higher in the renal transplant population as a result of heavy immunosuppression use. Misdiagnosis of melanoma can also create psychological and financial impact on these individuals. No studies so far have evaluated the extent of harm in relation to any of the recommended skin cancer screening tools in both the transplant and general populations.

Cost-Effectiveness of Skin Cancer Screening. The incremental cost-effectiveness ratio for skin cancer screening using total body skin examination by expert dermatologists was estimated to be $29,170 per LYS (66). This is comparable to most established screening programs. This analysis is based on the assumption that the incidence of late-stage melanomas will decrease with periodic skin cancer screening. It is the savings from treating high-grade melanomas that offset most of the costs of screening. This assumption, however, has not been proven in RCT.

Recommendation for Renal Cancer Screening

Screening for renal carcinoma is not recommended in the general population. The incidence of renal cell carcinoma is increased in renal transplant recipients and, in particular, recipients with acquired cystic disease of the kidneys (67). The AST, however, also found no evidence to support regular screening using ultrasonography or other radiology and urine cytology in renal transplant recipients.

Are the Recommendations Valid? Ultrasonography is thought to be the instrument of choice because it is relatively inexpensive, noninvasive, and easily accessible, yet no studies have assessed its efficacy and accuracy as a screening test. Renal ultrasonography is insensitive in detecting small lesions; its effectiveness as a screening tool to detect early-stage disease is questionable, especially in abnormal end-stage kidneys, some of which will have acquired cystic disease.

Harms from Renal Cancer Screening. Findings of an abnormality with ultrasonography screening will invariably lead to biopsies for histologic confirmation of disease. False-positive results will result in unnecessary invasive diagnostic procedures. Potential adverse events from biopsies include major and minor bleeding, pain, and infections. Major bleeding events can lead to graft dysfunction and loss. The psychological impact of receiving a diagnosis of a serious malignant disease is enormous on an individual. It can lead to unwanted anxiety and stress on both the patients and their families.

Cost-Effectiveness of Renal Cancer Screening. There are no data on the cost-effectiveness of renal carcinoma screening in both the renal and general populations. Cost-effectiveness, treatment outcomes, and benefits must be considered before promoting the use of expensive, potentially harmful diagnostic and screening procedures.

Recommendations for Lung Cancer Screening

Most of the American cancer screening guidelines also found insufficient evidence to recommend for or against lung cancer screening using chest x-ray, sputum cytology, and low-dosage computed tomography (CT) in the general population (18,33,68–70). There is no recommendation for population lung cancer screening in average-risk, asymptomatic individuals in Australia and New Zealand. Screening for lung cancers is also not recommended in renal transplant population.

Are the Recommendations Valid?

None of the six RCT in the general population using chest x-rays alone or combined with sputum cytology demonstrated mortality benefits in the screened populations (71). In fact, two of the trials showed that lung cancer mortality was significantly greater in the group with more frequent chest x-ray screenings than less intense screening after a longer follow-up period (72,73). There is now emerging evidence from observational studies to suggest that low-dosage spiral CT increases the detection rate of stage I lung cancer and 5-yr survival in high-risk individuals (74). This finding, however, may represent overde-
tection and lead-time bias with no real benefit in overall cancer-specific mortality. One large RCT is in progress, with the aim to provide an unbiased assessment of lung cancer screening with this potential screening tool (75).

Harms from Lung Cancer Screening. Abnormalities such as noncalcified nodules detected on radiology will result in additional testing: High-resolution CT, positron emission tomography scanning, bronchoscopy, lung biopsy, and resection. These procedures are costly and invasive and are associated with diagnostic- and treatment-related complication rates. Greater effort is required to limit the extent of false-positive and -negative results. Further investigation is needed to evaluate the risk for lung cancer from excessive radiation exposure, the issues of overde-
tection, and the emotional aspect of a false-positive and ambiguous test result among the transplant and general populations.

Cost-Effectiveness of Lung Cancer Screening. An economic analysis was performed to assess the cost-effectiveness of annual chest x-ray screening for lung cancer in the general population using parameter estimates from the four RCT. The base model showed an ICER of $20,000/LYS (76). This analysis is based on the assumption that lung cancer screening using annual chest radiography reduces cancer-specific mortality by 18%. The validity of this assumption is questionable when none
of the trials showed any mortality benefits. Although there is evidence to demonstrate that the stage distribution is much more favorable in the screened groups, it is not justifiable to assume that the effect of the stage shift correlates to the changes in life expectancies of the screened individuals as held in the model.

**Recommendation for Hepatocellular Carcinoma Screening**

Screening for hepatocellular carcinoma (HCC) is not recommended for average-risk individuals in the general population. For the high-risk population, periodic α-fetoprotein testing and ultrasound every 6 to 12 mo may be useful to detect HCC at an early stage (13). The British Society of Gastroenterology suggested that screening be considered in both genders with established cirrhosis secondary to hepatitis B virus, hepatitis C virus, and genetic hemochromatosis (14). The absolute risk for having HCC in women with alcoholic and primary biliary cirrhosis as well as individuals with cirrhotic livers associated with autoimmune hepatitis and primary sclerosing cholangitis is relatively low. If screening is proposed, then it should be performed every 6 mo with α-fetoprotein and abdominal ultrasound (14).

The AST made no firm recommendation for HCC screening in renal transplant recipients. They concluded the use of α-fetoprotein and abdominal ultrasound may be useful in the early detection of HCC only in the high-risk groups.

**Are the Recommendations Valid?**

A systematic review that included only two RCT evaluated the effectiveness and accuracies of HCC screening in patients with hepatitis B surface antigen in the general population using α-fetoprotein and/or abdominal ultrasonography on a biannual basis (77–79). None of the trials showed significant improvement in HCC mortality after initial follow-up, and neither of them assessed all-cause mortality.

Test accuracies, calculated from these trials, showed that the overall sensitivity and specificity for α-fetoprotein, with a cutoff point at 20 ng/L, ranged between 64.3 to 68.6% and 91 to 95%, respectively (78). Ultrasonography performed better than α-fetoprotein with the overall sensitivity and specificity between 71.4 to 84.3% and 93.8 to 97%, respectively (78). When α-fetoprotein and ultrasonography were used in combination, the sensitivity was 60% and specificity was 95% (78). It is apparent that neither method is ideal because both tests confer high false-positive and -negative rates. Similar to most other cancers, there is no evidence to suggest for or against HCC screening in the general population among high-risk individuals is inconclusive.

**Harms from HCC Screening.** None of the randomized controlled trials considered harms created by HCC screening. The diagnosis of HCC carries a significant psychologic and physical burden to an individual. Screening is only worthwhile if the diagnosis is correct and there is effective treatment to improve overall mortality outcomes. Based upon limited data, the proposed screening tool is far from perfect. Surgical intervention such as liver transplantation and surgical resection might be favorable for early stage cancer but it carries significant postoperative complications, especially from acute hepatic decompensation, bleeding and infections. False-assurance created from false-negative tests is another concern. It is often difficult to diagnose small lesions on ultrasonography especially in the case of cirrhotic nodular liver. HCC is a disease with rapid progression. It is highly aggressive, slight delay in treatment can render the disease incurable.

**Cost-Effectiveness of HCC Screening.** There is limited information regarding the cost-effectiveness of HCC screening in the general population and none in the renal transplant population. The ICER of annual screening with α-fetoprotein and ultrasonography compared with no screening varied between $23,034 and $26,689 per quality-adjusted life-year in two cost-utility studies (80,81), whereas in others, it ranged between $112,993 and $284,000/LYS (82,83). The cost-effectiveness of HCC screening in the general population among high-risk individuals is inconclusive.

**Recommendation for Prostate Cancer Screening**

Prostate cancer screening remains debatable in both the general and renal transplant populations. The US Preventive Services Task Force found no evidence to recommend for or against routine prostate cancer screening using prostate-specific antigen (PSA) and digital rectal examination (DRE) in average risk individuals (84). The American Cancer Society recommended annual screening with PSA and DRE in men who are older than 50 yr and have a life expectancy of at least 10 yr (18). The American College of Physicians made no firm suggestions about prostate cancer screening but recommended that information about the risks and benefits of screening be given to each person by the health care provider and that the decision to screen be individualized (85). The AST and the EBPG encourage annual prostate cancer screening with DRE and PSA measurement in all male renal transplant recipients who are older than 50 yr and have a life expectancy of at least 10 yr (10,12).

**Are the Recommendations Valid?** The benefits of prostate cancer screening in renal transplant recipients have not been assessed in any studies. Two RCT, conducted in North America and Europe, evaluated the effectiveness of prostate cancer screening in average-risk men who were ≥50 yr using PSA and DRE in the general population. In the Quebec trial, there was a 62% reduction of cancer-related mortality in the screened group (86). In the Norrkoping study, there were no significant differences in prostate cancer-related mortality and all-cause mortality in the screened population (87). The inconsistencies between the two trials could be related to the method of randomization, potential contamination of the unscreened group by opportunistic screening, and the poor participation rate in one of the trials. When these two trials were later assessed in a systematic review, they did not show an improvement in prostate cancer-related mortality and morbidity (88).

PSA and DRE have been used as the screening tool for prostate cancers in the past decade. A number of observational studies have evaluated the test accuracies of these tests. Most of these studies were flawed with verification biases whereby only those with a positive PSA or DRE finding were investigated by the reference standard, prostate biopsies. The overall pooled sensitivity, specificity, and positive PPV for PSA examined by a recent meta-analysis, with the accepted cutoff level of...
It is clear that, despite the difficulty of establishing primary
enabling both the treating physicians and patients to make
tions should clearly quantify the risks and benefits of screening,
ulation must be assessed for applicability to this population
tion here, however, has not been thoroughly assessed in this
there is sufficient evidence to show that cancer risk increases in
the renal transplant population. Screening of all cancers men-
Cancer is a major cause of death after renal transplantation, and
Conclusions

Cost-Effectiveness of Prostate Cancer Screening

Decision analytical models have shown that prostate cancer
screening might be cost-effective on the basis of favorable as-
sumptions derived from observational studies. The ICER var-
ed between $12,500 and $65,000/LYS, depending on the age
group and intervals of screening (93).

Despite the lack of proven benefits from RCT directed spe-
cifically to this subpopulation, screening for prostate cancers
using PSA measurement is now routine in most pre- and pos-
trenal transplant practices. Studies have shown that dialysis
and ESKD do not affect the PSA levels. It is not clear whether
the same applies to renal transplant recipients. Without evi-
dence from good-quality RCT, it is unjustifiable to instigate
mass screening for prostate cancer in both the general and renal
transplant populations.

Disclosures

None.

References

1. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C: Cancer after
kidney transplantation in the United States. Am J Trans-
plant 4: 905–913, 2004

2. Vajdic CM, McDonald SP, McCredie MR, van Leeuwen
MT, Stewart JH, Law M, Chapman JR, Webster AC, Kaldor
JM, Grulich AE: Cancer incidence before and after kidney
transplantation. JAMA 296: 2823–2831, 2006

3. Andersson I, Janzon L, Siglussen BF: Mammographic
breast cancer screening—a randomized trial in Malmo, Swe-

4. Roberts MM, Alexander FE, Anderson TJ, Chetty U, Don-
nan PT, Forrest P, Hepburn W, Huggins A, Kirkpatrick AE,
Lamb J, et al.: Edinburgh trial of screening for breast can-

5. Barratt A, Irwig L, Glasziou P, Cumming RG, Raffle A,
Hicks N, Gray JA, Guyatt GH: Users' guides to the medical
literature: XVII. How to use guidelines and recommenda-
tions about screening. Evidence-Based Medicine Working


7. Wilson MC, Hayward RS, Tunis SR, Bass EB, Guyatt G:
Users' guides to the Medical Literature. VIII. How to use
clinical practice guidelines B what are the recommenda-
tions and will they help you in caring for your patients?
The Evidence-Based Medicine Working Group. JAMA 274:
1630–1632, 1995

8. Lord SJ, Irwig L, Simes RJ: When is measuring sensitivity
and specificity sufficient to evaluate a diagnostic test, and
when do we need randomized trials? Ann Intern Med 144:
850–855, 2006

9. EBPG Expert Group on Renal Transplantation: European
best practice guidelines for renal transplantation. Section
IV: Long-term management of the transplant recipient. IV.

>4 ng/ml, were 72.1, 93.2, and 25.1%, respectively. The results
for DRE were 53.2, 86.2, and 17.8%, respectively (88). Test
performance of PSA and DRE has not been assessed in renal
transplant recipients. In patients who had ESKD and were on
dialysis, the overall test sensitivity of PSA was poor, with an
estimated test sensitivity of 66.7% and PPV of 50% using a
standard cutoff of >4 ng/ml (89).

Two large, well-structured, and well-powered RCTs are now
under way in the United States and Europe, involving >100,000
people in each study to assess the effectiveness and efficacies
of prostate cancer screening in average-risk individuals (90,91).
The uncertainties and controversies may be resolved when the
results of these trials are reported in the next decades.

Harms of Prostate Cancer Screening. Concern about the
consequences of overdetection and overdiagnosis is most ap-
licable in prostate cancer screening. Approximately 10 to 15%
of men will develop clinically significant prostate cancer in
their lifetime, but approximately 40% of men who are older
than 80 yr have incidental prostate cancer found at autopsy
(92). The significance of diagnosing and treating inconsequen-
tial disease is unknown. In most instances, men are reluctant to
"watch and wait" after the detection of early-stage cancers, and
clinicians are obliged to treat for the fear of medicolegal con-
sequences. The treatment itself, however, is not at all benign.
Complications such as erectile dysfunction, urinary/fecal in-
continence, and radiation cystitis can have major adverse phys-
ical and psychological impacts on these individuals.

Acknowledgments

G.W. conceived and designed the study, performed the literature
search, analyzed and interpreted the results, and wrote the manuscript;
J.R.C. conceived and designed the study, advised on the presentation of
results, analyzed the results, and revised the manuscript; J.C.C. con-
ceived and designed the study, advised on the literature search, ana-
yzed and interpreted the results, advised on the presentation of results,
and revised the manuscript.


Cancer Screening: Post-trial follow-up of lung cancer deaths up to year 15 since enrollment. Cancer 89[Suppl]: 2363–2368, 2000

74. Henschke CI: Early lung cancer action project: Overall design and findings from baseline screening. Cancer 89[Suppl]: 2474–2482, 2000


