Abstract

The incidence of renal cell carcinoma (RCC) has risen worldwide over the past few decades, and this has been associated with a stage shift. Survival outcomes of RCC depend largely on the stage at diagnosis. Although overall mortality has stabilized or declined in most countries, survival remains poor in late-stage disease, suggesting early detection may improve overall survival outcomes. A number of potential candidate screening tools have been considered (including urinary dipstick, blood- and urine-based biomarkers, ultrasound, and computed tomography (CT)), though it may be that a combination of these approaches may be optimal. Ultimately, the sensitivity and specificity of the chosen screening tool will determine the rate of false positives and false negatives, which must be minimized. One of the key challenges is the relatively low prevalence of the disease, which might be overcome by performing risk-stratified screening or screening for more than one condition (such as combined lung and kidney cancer screening). Both approaches have been shown to be acceptable to the general public, and they may maximize the efficiency of screening while reducing harms. Indeed, quantifying benefits and harms of screening is key (including the impact on overdiagnosis and quality of life). Whether screening for RCC will lead to a stage shift and the impact on survival are the decisive missing pieces of information that will determine whether the screening program might be adopted into clinical practice (along with feasibility, acceptability, and cost-effectiveness).

Epidemiology and Risk Factors for RCC

Incidence and Risk Factors

Renal cell carcinoma (RCC) is the 9th most frequently diagnosed cancer in men and the 14th most common in women globally, accounting for 2.2% of all new cancer diagnoses (Table 1)[1]. The incidence of RCC demonstrates geographic variability (Figure 1)[2,3]. The International Agency for Research on Cancer (IARC), established in 1965 by the World Health Assembly, provides comprehensive information on global cancer epidemiology by aggregating data from 343 population-based cancer registries in 65 countries[4]. The registry data is currently available online at the Global Cancer Observatory as the GLOBOCAN database[2]. According to the GLOBOCAN 2020 report, the age-standardized incidence of kidney cancer is highest in Northern America, followed by Europe, Oceania, Latin America and the Caribbean, Asia, and Africa (Figure 1). The incidence of RCC has generally increased over time in both sexes, and is predicted to continue to rise over the next 15 years, although there is some variability across countries[2,3].
The geographic distribution and rising incidence of RCC have been partially attributed to variation in risk factors for the disease as well as differences in healthcare delivery systems, as detailed below[5–7].

A number of modifiable and nonmodifiable risk factors for RCC have been identified (Table 2). The aging population and rising prevalence of certain risk factors (such as obesity, hypertension, and diabetes) contribute to increasing rates of the disease[5–7]. In addition, increased incidental detection reflects the widespread use of abdominal imaging. For example, in the United States, it is estimated that 43% of individuals aged 65–85 years on Medicare undergo either thoracic or abdominal computed tomography (CT) in a 5-year period, and for every 1000 CT scans performed there are 4 additional nephrectomies[8]. Additionally, 2 studies have shown a statistically significant increase in the number of renal cancers detected among newly insured patients secondary to widening access to care through expansion of healthcare insurance[9,10].

Incidental detection has also contributed to a stage shift (i.e., detection of disease at an earlier stage), which was noted until the mid-2000s and has subsequently stabilized[11–13]. Clinical stage 1 tumors accounted for 43% of all kidney cancers diagnosed in 1993; the percentage increased to 57% in 2004[11] and leveled off around 70% after 2007, although the size of localized tumors continued to decline[12]. Overall, between 1993 and 2004, 50.6%, 26.7%, and 22.7% of kidney cancer patients were diagnosed with stage I, stage II or III, and stage IV, respectively[11]. In contrast, between 2004 and 2015, 70.3%, 10.5%, 8.3%, and 11.0% of patients were diagnosed with stage I (including 47.5% stage Ia and 22.8% stage Ib), stage II, stage III, and stage IV, respectively, highlighting a significant increase of stage I as well as a decrease of stage IV RCC[12].

### Mortality

The crude mortality rate of kidney cancer was 13th in men and 14th in women (Table 1; Figure 2)[1]. Europe has the highest age-standardized mortality rate, followed by Northern America/Oceania, Latin America and the Caribbean, Asia, and Africa (Figure 2). The age-standardized rate and the cumulative risk for kidney cancer death have been stabilizing in many countries, and have declined particularly in Europe and Northern America during the past one to 2 decades in both sexes[2,14]. Survival outcomes of RCC depend largely on the stage at diagnosis. The most recent report based on the National Cancer Database in the United States showed that the 5-year survival rate was 93%, 70%, and 13% in patients with localized, regional, and distant RCC, respectively[15]. In this report, the mortality data were collected by the National Center for Health Statistics[15]. Similar survival outcomes were also observed in the United Kingdom; 5-year survival was 87% in stage I compared to 12% in stage IV RCC[16]. The decline in kidney cancer mortality may, therefore, be related to earlier diagnosis, as well as improved treatment strategies and recent advances in systemic therapy[12,17].

### Population Screening

#### Rationale for Screening

The relatively large proportion of patients with RCC who are diagnosed at a late, advanced, or metastatic stage due to the absence of symptoms and the poor survival in this group are the main drivers for the need to improve the early detection of RCC. Initiatives to raise public awareness of hematuria have not been successful in improving detection of RCC[18], suggesting that a more systematic identification approach may be necessary. Screening for RCC has the potential to improve survival outcomes by enabling earlier diagnosis and treatment[19,20]. No randomized controlled trials (RCTs) of screening for RCC have been performed and due to insufficient evidence, international urology and oncology associations have yet to publish guidelines on this topic[21–27]. Screening and early detection of RCC have been identified as a key research priority in 3 independent priority-setting initiatives[28–31], and patient groups have been vocal in their desire to champion this agenda[32]. The “sojourn time,” also known as the “preclinical period,” refers to the length of time during which an individual with RCC has not yet received a diagnosis, and would therefore benefit from early detection via screening. Cancers with very short or very long sojourn times are not ideal screening candidates. Imaging studies have suggested the sojourn time for RCC is between 3.7 and 5.8 years[33]. Scelo et al. demonstrated raised kidney injury molecule-1 (KIM-1) plasma levels up to 5 years prior to RCC.
### TABLE 1.
Age-standardized rate and cumulative risk of kidney cancer incidence and mortality (GLOBOCAN 2020 report) [1]

<table>
<thead>
<tr>
<th>Region</th>
<th>Incidence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ASR, per 100 000(^a)</td>
<td>Cumulative risk, %(^a)</td>
</tr>
<tr>
<td><strong>Worldwide</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6.1</td>
<td>1.45</td>
</tr>
<tr>
<td>Female</td>
<td>3.2</td>
<td>0.76</td>
</tr>
<tr>
<td>Both sexes</td>
<td>4.6</td>
<td>1.06</td>
</tr>
<tr>
<td><strong>Europe</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13.1</td>
<td>2.78</td>
</tr>
<tr>
<td>Female</td>
<td>6.4</td>
<td>1.36</td>
</tr>
<tr>
<td>Both sexes</td>
<td>9.5</td>
<td>1.96</td>
</tr>
<tr>
<td><strong>Northern America</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16.1</td>
<td>3.23</td>
</tr>
<tr>
<td>Female</td>
<td>8.6</td>
<td>1.69</td>
</tr>
<tr>
<td>Both sexes</td>
<td>12.2</td>
<td>2.39</td>
</tr>
<tr>
<td><strong>Latin America and the Caribbean</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6.3</td>
<td>1.37</td>
</tr>
<tr>
<td>Female</td>
<td>3.3</td>
<td>0.74</td>
</tr>
<tr>
<td>Both sexes</td>
<td>4.7</td>
<td>1.02</td>
</tr>
<tr>
<td><strong>Oceania</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12.4</td>
<td>2.83</td>
</tr>
<tr>
<td>Female</td>
<td>5.4</td>
<td>1.27</td>
</tr>
<tr>
<td>Both sexes</td>
<td>8.8</td>
<td>2.00</td>
</tr>
<tr>
<td><strong>Asia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3.8</td>
<td>0.89</td>
</tr>
<tr>
<td>Female</td>
<td>1.9</td>
<td>0.45</td>
</tr>
<tr>
<td>Both sexes</td>
<td>2.8</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Africa</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2.1</td>
<td>0.48</td>
</tr>
<tr>
<td>Female</td>
<td>1.5</td>
<td>0.24</td>
</tr>
<tr>
<td>Both sexes</td>
<td>1.8</td>
<td>0.34</td>
</tr>
</tbody>
</table>

**ASR:** age-standardized rate.

\(^a\) The age-standardized rate (ASR) was adjusted to the world standard population.

\(^b\) The cumulative risk was the probability of kidney cancer development or death in a lifetime defined as 0–74 years.

FIGURE 1.
Age-standardized rate of kidney cancer incidence


FIGURE 2.
Age-standardized rate of kidney cancer mortality

### TABLE 2.
Modifiable and nonmodifiable risk factors for RCC

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative risks (RRs) and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Modifiable factors</strong></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>Established risk factor for RCC[34–37]</td>
</tr>
<tr>
<td></td>
<td>RR 1.31 (95% CI, 1.22–1.40) for smokers versus nonsmokers[34]</td>
</tr>
<tr>
<td>Obesity</td>
<td>Established risk factor for RCC[35,37–39]</td>
</tr>
<tr>
<td></td>
<td>RR 1.77 (95% CI, 1.68–1.87) for obesity (BMI ≥ 30) versus a normal BMI[39]</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Established risk factor for RCC[37]</td>
</tr>
<tr>
<td></td>
<td>RR 1.70 (95% CI, 1.30–2.22) for patients with hypertension vs. those without hypertension[37]</td>
</tr>
<tr>
<td></td>
<td>Meta-analysis reported 67% increased risk in patients with hypertension[40]</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Controversial whether diabetes is an independent risk factor for RCC due to potential confounders (smoking, obesity, and hypertension)[7,41]</td>
</tr>
<tr>
<td>Diet</td>
<td>Meat: potential risk factor for RCC; may be partially related to the carcinogens formed in the cooking process[42,43]</td>
</tr>
<tr>
<td></td>
<td>Fruit and vegetables: may be protective (particularly for cruciferous vegetables)[44,45]</td>
</tr>
<tr>
<td></td>
<td>Alcohol: may be protective; an inverse relationship between moderate alcohol intake (&lt; 60 g/day) and RCC risk is reported[46,47]</td>
</tr>
<tr>
<td>Occupation</td>
<td>Trichloroethylene: may modestly increase the risks of several cancers including RCC[48–50]; Toxicity is officially acknowledged by the Environmental Protection Agency in the United States</td>
</tr>
<tr>
<td>Drug exposure</td>
<td>Acetaminophen and NSAIDs other than aspirin: significantly associated with an increased incidence of kidney cancer[51]</td>
</tr>
<tr>
<td></td>
<td>Aspirin: No increase in RCC incidence[51]</td>
</tr>
<tr>
<td><strong>Nonmodifiable factors</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>RCC incidence increases with age[14]</td>
</tr>
<tr>
<td></td>
<td>Global crude incidence, per 100 000 = 4.3 in 40–49 years, 10.8 in 50–59 years, 20.3 in 60–69 years, and 29.6 in 70–79 years[1]</td>
</tr>
<tr>
<td>Sex</td>
<td>RCC incidence shows 2.1 male predominance across the world[1] (Table 1)</td>
</tr>
<tr>
<td></td>
<td>May be related to various confounders including modifiable risk factors of RCC (smoking, obesity, or hypertension) as well as intrinsic biological variances</td>
</tr>
<tr>
<td>Race</td>
<td>Racial disparities between black and Caucasian has been highlighted ASRs of kidney cancer incidence in black vs. white individuals, per 100 000 = 16.4 vs. 13.5 in males and 8.1 vs. 7.0 in females[2]</td>
</tr>
<tr>
<td></td>
<td>ASRs of kidney cancer incidence in black vs. white individuals, per 100 000 = 16.4 vs. 13.5 in males and 8.1 vs. 7.0 in females[2]</td>
</tr>
<tr>
<td>Family history</td>
<td>RR 2.2-fold when patients have RCC history in any-degree relatives[52]</td>
</tr>
<tr>
<td></td>
<td>RR 4.3-fold when patients have RCC history in first-degree relatives[52]</td>
</tr>
</tbody>
</table>

*ASR: age-standardized rate; BMI: body mass index; CI: confidence interval; NSAID: nonsteroidal anti-inflammatory drug; RCC: renal cell carcinoma.*
disease, diabetes, infection, etc). The high volume of diseases associated with proteinuria or glycosuria (renal (including renal stones, cysts, etc.) as well as medical may identify a large number of nonmalignant urological have bladder cancer [63]. Conversely, urinary dipstick hematuria are found to have RCC and 5% are found to population[64,67]; however, <1% of individuals with NV hematuria may be as high as 20% to 30% in the general number of false negatives. The prevalence of hematuria not have hematuria, meaning there would be a large number of incidental findings preclude this as a cost-effective screening strategy for RCC.

Urinary biomarkers would represent the ideal screening tool; however, to date none are validated or approved for use in clinical practice[68]. A number of different analytes have been considered, including urinary proteins, cell-free tumor DNA, microRNAs, and exosomes. Perhaps the most well-studied group is urinary proteins, including aquaporin-1, perilipin-2, carbonic anhydrase-9, Raf-kinase inhibitory protein, nuclear matrix protein-22, 14–3–3 Protein β/α, and neutrophil gelatinase-associated lipocalin[68]. Aquaporin-1 and perilipin-2 have been evaluated in a prospective study of 720 patients undergoing screening CT, 80 healthy controls, and 19 patients with RCC. In this cohort, these 2 biomarkers used in combination achieved an area under the curve (AUC) of > 0.99 for RCC[69]. Although these 2 proteins may be good markers for clear cell renal cell carcinoma (ccRCC) and papillary renal cell carcinoma (pRCC), levels are low or negative in chromophobe renal cell carcinoma (chRCC), meaning that screening would miss these cancers[19]. Further prospective validation in an independent cohort is warranted.

**Blood Tests**

Blood-based tests represent another potentially useful option due their relative public acceptability and presumed relatively low cost. Analytes similar to those identified in urine may be used, such as proteins, circulating tumor DNA (ctDNA), microRNAs, and exosomes. KIM-1 is a glycoprotein that reflects injury to the proximal convoluted tubule of the kidney (from which ccRCC and pRCC are derived). KIM-1 blood levels may be elevated 5 years prior to a diagnosis of RCC[53]. One of the main disadvantages is the low specificity of KIM-1 (levels may be elevated in kidney injury). Furthermore, KIM-1 levels are not elevated in patients with renal tumors derived from the distal nephron (e.g., chRCC and collecting duct RCC), limiting applicability as a screening tool. Cancer screening using ctDNA has recently received significant media attention and has entered large-scale validation studies[70–72]. A number of studies have been published evaluating ctDNA for the simultaneous detection of multiple cancer subtypes with the aim of pan-cancer screening[70,73–75]. Although initial reports evaluating mutations[76] and methylation patterns[74] in ctDNA suggested that patients with RCC may have lower levels of ctDNA than those with other malignancies, more recent reports evaluating DNA methylation appear more promising[77]. Nuzzo et al.[77] evaluated ctDNA methylation using cell-free methylated DNA immunoprecipitation and high-throughput sequencing (cfMeDIP–seq) in a case-control study. The
study cohort included 99 ctDNA samples from patients with RCC (of which 33% were from patients with stage I–II disease), 21 samples from patients with stage IV bladder cancer, and 28 healthy controls. The overall AUC for the detection of RCC was 0.99, suggesting ctDNA may be detected in patients with RCC across the spectrum of disease severity, raising the possibility that in future this could potentially be used to enable earlier disease detection.

Unfortunately, thus far, neither urine- nor blood-based biomarkers have achieved sufficient sensitivity and specificity required for implementation in clinical practice. Further research on minimally invasive biomarkers as a screening tool, in prospective cohorts, is warranted.

Ultrasound
Ultrasound is perhaps the most well-studied screening method for RCC, with a number of observational studies published in the 1990s and early 2000s[78–85]. The main drawback is that accuracy is dependent on operator experience, anatomical factors (including obesity and overlying bowel gas), and lesion size. There is a potential for false negatives, as ultrasound can detect 85% to 100% tumors > 3 cm in size, but only 67% to 82% of tumors of 2–3 cm in size[86,87]. Advantages of ultrasound include the relative acceptability by the general public, as it is pain-free and noninvasive (compared to blood tests). Ultrasound is widely available, does not involve ionizing radiation, and is relatively inexpensive compared to CT. Furthermore, focused renal ultrasound may be performed, imaging the kidneys alone rather than the entire abdomen, therefore reducing the time and cost of the scan and avoiding incidental detection of indeterminate lesions in other abdominal organs, which may require additional investigation with associated costs. Another potential advantage is the opportunity to combine screening for renal cancer with the existing abdominal aortic aneurysm (AAA) screening program, currently underway in a number of countries[88–90]. A combined approach would reduce the overall cost of the screening intervention and maximize cost-effectiveness, although currently AAA is only recommended for men and not women. To the best of our knowledge, Malaeb et al.[85] is the first and only study to explore the combined screening of RCC and AAA, demonstrating this is a feasible approach that is well tolerated by patients. Although this study is promising, none of the ultrasound studies were randomized in nature, meaning the impact of the intervention on survival remains unknown.

Computed Tomography
Use of CT has increased in recent decades due to technological advances (enabling increased resolution, reduced scanning times, and lower radiation dose), increasing availability and reducing costs[8,91]. Contrast-enhanced CT is the gold-standard diagnostic imaging technique to evaluate small renal masses in patients with suspected RCC (e.g., if a mass is identified on ultrasound or there is visible hematuria). Contrast uptake can enable the differentiation between benign and malignant disease, and visualization of tumor and vessel anatomy that can guide operative management approaches. However, the utility of contrast-enhanced CT as a screening tool in the general population is limited by the use of contrast (which may be nephrotoxic), the relatively high radiation dose, and cost, particularly given the low prevalence of RCC. However, low-dose unenhanced CT has the advantage of providing less radiation dose and no contrast.

Whole-body CT has been proposed as a potential screening tool for the combined detection of multiple malignant and nonmalignant diseases (e.g., abdominal cancers, AAA, etc.). Although a number of studies have been performed, the main drawback of performing whole-body scans is the high number of incidental findings, false positives, and findings of unknown clinical potential. For example, Millor et al.[92] reviewed 6516 whole-body screening CTs (which included unenhanced chest CT, enhanced abdominal CT, cardiovascular, and bone assessments). Fewer than 2% of individuals had normal scans, meaning that > 98% had to undergo further investigations with significant costs, burden to the health service, and anxiety for the individual. Only 1.5% of individuals were found to have a malignancy (35 of 96 were RCC). As a result, whole-body CT to screen for kidney cancer as a standalone test in an unselected population is unlikely to be a cost-effective strategy at present[93], though in future automated interpretation of imaging features using machine learning may increase the accuracy and feasibility of this strategy[95]. An alternative approach is to add low-dose noncontrast abdominal CT scans to the low-dose unenhanced chest CT scans currently being investigated for lung cancer screening. The Yorkshire Kidney Screening Trial (NCT05005195), currently underway, is a novel study and the first to evaluate the added benefit of screening for RCC by extending the low-dose chest CT to image the kidneys in 55–80-year-old smokers and ex-smokers undergoing lung cancer screening enrolled in the Yorkshire Lung Screening Trial[95]. It is postulated that combined lung and kidney cancer screening may maximize cancer detection rates while reducing costs.

Screening Population
The ideal population to whom screening for RCC should be offered is unknown. Meta-analyses have estimated that screening 1000 individuals using ultrasound would identify between 1 and 2 patients with RCC[78], while using CT would identify between 1 and 3 (the pooled
prevalence of RCC is 0.17% (95% CI 0.09–0.27%) and 0.21% (95% CI, 0.14–0.28%) in ultrasound and CT respectively) [33,78]. One of the main challenges is the relatively low prevalence of RCC. Indeed, a health economic analysis of screening for RCC using ultrasound identified prevalence of RCC as the greatest determinant of cost-effectiveness [96].

Risk-stratified screening may enable more efficient identification of RCC, focusing on high-risk individuals and therefore maximizing benefits while reducing costs and harms for those at low risk. A systematic review of risk-prediction models for RCC [97] identified 11 models that report performance measures and could potentially be used. Fewer than 20% (2 of 11) had been validated in an external population, highlighting one of the limitations of current models. The most commonly included factors were sex, age, smoking status, body mass index (BMI), and hypertension, which is consistent with the known data on risk factors for RCC. However, none of these risk factors are specific for RCC. Only one study considered genetic risk (i.e., single-nucleotide polymorphisms) and biomarker studies were characterized by a high risk of bias. The models identified in the systematic review were externally validated in >450,000 participants within the UK Biobank cohort [98]. Five models had reasonable calibration and discrimination, with an area under the receiver operating characteristic curve between 0.61 and 0.72. All the models performed less well in women, compared to men. Additionally, although the models were better at identifying individuals at high risk for RCC than age and sex alone, the improvement was small. Risk-prediction models for RCC based on genetic factors performed poorly compared to the best genetic risk models for other cancers, suggesting more research on this topic is needed [99]. Future incorporation of biomarkers into risk scores could improve performance.

Screening Implementation and Public Acceptability

If screening is demonstrated to improve disease-specific survival, it is crucial to consider implementation within the existing healthcare delivery system. The cost of screening is not limited to the intervention itself, but includes the associated costs of investigating incidental findings and the cost of treatment of diagnosed conditions. The cost-effectiveness of any screening intervention needs to be demonstrated prior to the screening program being accepted into clinical practice. Other important considerations are in regard to program delivery, including optimal screening location (e.g., primary care, secondary care, screening vans in public spaces), training an adequate workforce to deliver screening (e.g., ultrasound delivered by technicians vs. sonographers), and quality control (e.g., audit for laboratories undertaking biomarker work or facilities offering imaging).

Public acceptability of the program will also be key to ensure high attendance rates. A survey has shown that members of the general public would be “very likely” or “likely” to undergo each of the following screening tests: urine test, 94%; blood test, 90%; ultrasound, 90%; low-dose CT, 79%; and low-dose CT offered as part of lung screening, 95% [55]. In addition, 83% reported that tailoring the starting age of RCC screening based on a risk score incorporating phenotypic or genetic risk was acceptable, and 85% reported they would be more likely to attend screening if the risk score suggested they were high risk [100]. The high anticipated intention to attend screening and positive attitudes toward risk-stratified screening are promising.

Unknown Benefits and Harms

Although screening could have many potential benefits, there are still many unknowns that require further research (Table 3). Importantly, it is unclear whether screening would lead to increased RCC diagnoses (including a stage shift) in view of the high rates of incidental detection. Crucially, it is unknown whether screening leads to a survival benefit. Another main challenge relates to increased detection of small renal masses (SRMs, defined as <4 cm in diameter), which are difficult to characterize and therefore may lead to false positives or overdiagnosis of indolent lesions (Table 4). Ultimately, being able to clearly determine which SRMs require further investigation or treatment and developing pathways for the management of patients with SRMs based on competing risks are essential before any RCC population-based screening program can be implemented.

As screening is offered to a large number of asymptomatic individuals in order to detect only a small number of cancers, it is crucial to understand any quality of life (QoL) detriment associated with screening itself. None of the observational studies evaluating ultrasound screening for RCC assessed the impact on QoL [19]. There are a number of ways in which screening can cause harm (Table 4) [101–103]. These include physical harm, resulting from both the screening test and/or follow-up procedures; psychological harm, including increases in anxiety; treatment burden, including from subsequent invasive procedures and overdiagnosis; financial costs associated with travel and time off work to attend appointments and potential loss of earnings; social harm, resulting from social stigma or missing out on other activities; and dissatisfaction with health care.
**Future Directions**

In summary, the incidence of RCC has risen worldwide over the past few decades, and this has been associated with a stage shift. Survival outcomes of RCC depend largely on the stage at diagnosis. Although overall mortality has stabilized or declined in most countries, survival remains poor in late-stage disease, meaning that early detection could improve overall survival outcomes. A number of potential candidate screening tools are currently being investigated, though it may be that a combination of these approaches may be optimal. Ultimately, the sensitivity and specificity of the chosen screening tool will determine the rate of false positives and false negatives, which must be minimized. One of the key challenges is the relatively low prevalence of the disease, which might be overcome by performing risk-stratified screening or screening for more than one condition (such as combined lung and kidney cancer screening). Both approaches have been shown to be acceptable to the general public, and they may maximize the efficiency of screening while reducing harms. Whether screening for RCC will lead to a stage shift and the impact on survival are the decisive missing pieces of information that will determine whether the screening program might be adopted into clinical practice (along with feasibility, acceptability, and cost-effectiveness).

**TABLE 3.**

<table>
<thead>
<tr>
<th>Unknowns</th>
<th>Comments, challenges, and future direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>The ideal screening modality is unknown.</td>
<td>• Ideally a two-step approach would be adopted (such as for colorectal cancer screening), where an initial noninvasive test (e.g., urinary test) would be followed by a second, more advanced test (e.g., imaging).</td>
</tr>
<tr>
<td>The ideal screening population is unknown.</td>
<td>• The main challenge is the low prevalence of RCC, meaning that a large number of healthy individuals would have to be screened to identify only a small number of cases. • Risk-prediction models may identify individuals at high risk, therefore maximizing cost-effectiveness. However, existing models have a relatively low accuracy and are based on nonspecific risk factors.</td>
</tr>
<tr>
<td>Unknown whether screening for kidney cancer will translate into a survival benefit beyond length and lead time bias.</td>
<td>• No randomized controlled trials (RCTs) have been performed to date. • Ultimately, an RCT would be needed to demonstrate a survival benefit; however, due to the low prevalence of RCC, this would necessitate hundreds of thousands of participants with long-term follow-up, which is prohibitive.</td>
</tr>
<tr>
<td>Unknown whether screening will lead to increased detection and a stage shift (i.e., earlier detection) given high volume of abdominal imaging for other complaints and widespread incidental detection.</td>
<td>• It is estimated that 43% of individuals aged 65–85 years on Medicare in the United States undergo either a CT chest or CT abdomen over a 5-year period[8], meaning that it is unclear whether these individuals may benefit from further screening.</td>
</tr>
<tr>
<td>Unclear when to start screening and how often to screen.</td>
<td>• No premalignant lesion has been identified for RCC. • Thus far, studies have evaluated screening for RCC at a single time point rather than regular intervals[19].</td>
</tr>
<tr>
<td>Potential harms of screening and the impact on quality of life have not yet been fully quantified.</td>
<td>• See Table 4.</td>
</tr>
<tr>
<td>Unclear whether screening could be implemented in the current health service.</td>
<td>• Once the screening modality has been selected, further data will be needed on cost-effectiveness (based on a trial), feasibility, public acceptability, and potential uptake.</td>
</tr>
</tbody>
</table>

TABLE 4.  
Potential harms of screening for RCC  
The following potential harms may depend on the screening modality that is ultimately chosen

<table>
<thead>
<tr>
<th>Potential harms</th>
<th>Comment</th>
</tr>
</thead>
</table>
| False negatives                                      | • False negatives are associated with real harms and anxiety to the individual.  
• May erode public trust in the screening program and negatively affect attendance if the test is perceived to be inaccurate.                                           |
| False positives                                      | • Unfortunately, it is not possible to accurately differentiate benign from malignant SRMs using contrast-enhanced CT, the gold standard imaging investigation\[^{97,98}\].  
• Renal biopsy is often under-utilised due to inadequate service provision, lack of expertise or low perceived clinical benefit. Biopsy is non-diagnostic in \(\sim10\)% of cases\[^{99}\] and it can be particularly difficult to distinguish oncocytoma from eosinophilic variants of chRCC and ccRCC.  
• A meta-analysis demonstrated approximately 25% of renal biopsies reported as oncocytoma are found to be malignant following excision\[^{100}\]. Erring on the side of caution, patients with SRM are often offered surgery and as a result, approximately 20%-30% are found to have benign disease post-operatively, meaning they underwent unnecessary surgery, with associated morbidity and potential long-term effects on renal function\[^{101,102}\]. |
| Overdiagnosis and overtreatment of renal tumors that would not affect survival | • It is not possible to distinguish aggressive from indolent SRMs, meaning that screening could identify a large number of individuals with SRMs who would not benefit from treatment.  
• Increasing the use of active surveillance (which has been shown to be noninferior to primary intervention) especially in patients with comorbidities who may have a limited life expectancy, could reduce overtreatment\[^{62}\].  
• Recently, a growing number of observational studies are being performed that are increasing our understanding of the natural history of disease\[^{62}\]. |
| Incidental findings                                  | • High cost of further investigations.  
• May have indeterminate clinical potential and result in increased patient anxiety.  
• However, imaging-based screening may identify additional conditions (such as other abdominal cancers or AAA) that could benefit patients. |
| Anxiety and worry                                     | • Resulting from both the screening test and/or follow-up procedures.                                                                                                                                 |

References


Kidney Cancer Screening and Epidemiology


