Epidemiology and Screening in RCC

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Epidemiology

Renal cell carcinoma (RCC) is the sixth most common cancer in men and tenth most common cancer in women worldwide [1]. Incidence is 15 times higher in developed countries compared to the developing world [2] and RCC is one of the fastest accelerating cancers. Indeed, RCC incidence rates have increased by 47% in the last 10 years [1]. The rise in incidence has been postulated to be, at least in part, due to rising rates of risk factors such as obesity and the aging population [2–4]. In addition, a major contributor is the increased use of abdominal imaging for the investigation of other abdominal symptoms, which leads to incidental detection [5]. On one hand, survival rates are poor (10 year overall survival: 52%) [6] meaning there is a drive to improve patient outcomes (Fig. 1) [8]. On the other hand, although the overall incidence is increasing, the incidence of metastatic disease and mortality rates have remained static, suggesting that a proportion of detected cancers will not impact patient survival and have led to concerns regarding overdiagnosis [9]. RCC mortality continues to rise in Eastern Europe however [10]. These epidemiological data highlight the need for improved understanding of the pathophysiology of RCC.

Risk Factors

The main risk factors and associated relative risks (RR) for RCC are [1, 6, 11, 12]:

- Increasing age: peak incidence is 60-70 years
- Male sex (RR = 1.5 to 2)

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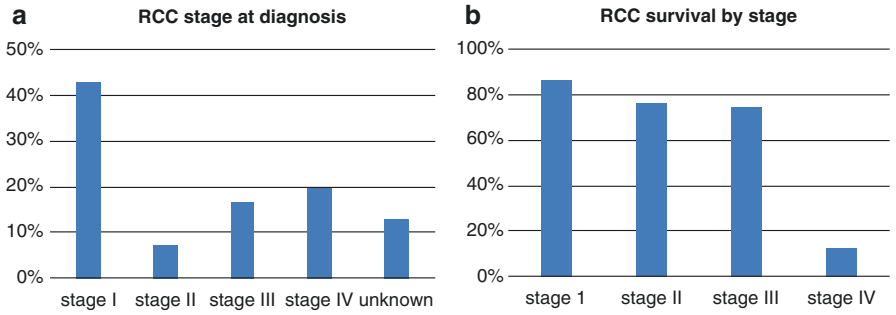

Fig. 1 (**a** and **b**): Stage at diagnosis (**a**) and five-year survival by stage (**b**). (**a**) stage at diagnosis in England for patients diagnosed between 2012 and 2017 [7]. (**b**) Five-year survival by stage in the UK for 2013–2017 [6]

- Race: Higher risk in African Americans compared to Caucasians
- Obesity (RR = 1.7 for BMI >35 kg/m^2 vs <25 kg/m^2)
- Smoking (RR = 1.3 to 1.5 smokers vs never smokers)
- Hypertension (RR = 1.7)
- Renal disease: acquired cystic kidney disease, end stage renal failure and renal transplant (RCC affects the native kidney).
- Family history
  - A number of inherited rare cancer syndromes predispose to RCC. In sporadic RCC, having an affected first degree relative is associated with a RR of 2. A number of single nucleotide polymorphisms (SNPs) have been identified, which can be combined into a polygenic risk score (three fold increased risk of RCC in the highest decile compared to the lowest decile) [13].
- Diabetes type 2 (RR = 1.6)

Moderate alcohol consumption and high physical activity are considered protective [14–17]. A number of potential risk factors have been identified which are less well established and require further research. According to the International Agency for Research on Cancer (IARC) exposure to trichloroethylene, gamma and x radiation are associated with an increased risk of RCC; whilst other occupational exposures have limited evidence [18]. Conflicting results have been observed for: renal stones, parity/hormonal factors, fruit/vegetable intake and analgesic use.

Rationale for Screening

Earlier detection and screening for RCC has been identified as a key research focus by two independent priority setting initiatives, as well as patient advocacy groups [19–22]. This is because the disease is often asymptomatic, resulting in delayed diagnosis, and there is a clear association between stage at detection and survival. In fact, 60% of cases of RCC are asymptomatic at diagnosis, and this rate is even

higher (87%) for stage T1a RCC, which have the most favourable prognosis (cancer specific survival >95% in surgically treated T1a RCC) [23, 24]. Approximately 20–25% cases have metastases at diagnosis, and five-year cancer specific survival for these individuals is 12% [6, 7].

It has therefore been postulated that earlier diagnosis, and treatment of the disease at a curable stage, would lead to overall improved survival rates. In addition, the relatively high cost of systemic therapies for advanced disease means that investing resources into screening could potentially be cost-effective.

However, no randomised controlled trials (RCT) have been performed to date, so it is yet unclear what the ideal screening modality and target population would be, and if screening would impact survival [8, 11]. Any screening programme must be considered in the context of the Wilson and Jungner criteria and weigh up potential benefits and harms (Table 1) [28].

Screening Test

A number of modalities have been proposed as potential screening tools (Table 2). These include primary screening with imaging or a staged approach, where a non-invasive blood or urine test (such as urinary dipstick or biomarkers) may be used to identify individuals who warrant further investigation. A number of studies were performed in the 1990s evaluating ultrasound as a screening tool, however none were randomised in nature, nor powered to assess survival (Table 2). Screening using ultrasound or low dose CT remain the most likely candidates. Offering screening for RCC in combination with other existing or possible future screening programs (e.g. ultrasound for aortic aneurysms or CT for lung cancer) may increase cost-effectiveness and is viewed positively by the public [48].

Although a number of blood and urinary biomarkers (such as proteins, micro RNAs, circulating tumour DNA and circulating tumour cells) have been studied, none have been validated and adopted for use in clinical practice. Biomarker studies are heterogeneous, adopt small sample sizes, lack external validation and on occasion generate conflicting results [47]. A main limitation of existing biomarkers has been the lack of sensitivity and specificity for RCC. In addition, studies use techniques such as western blotting (e.g. for proteins) or expensive next generation sequencing approaches (e.g. for circulating tumour DNA) which are not scalable in the context of a population screening program. Further research in this fields remains promising.

The Screening Population

The ideal screening population has yet to be determined. One potential strategy would be to screen individuals based on age and sex. Further work should elucidate the ideal starting age, and if this should be different for men and women. One of the

Table 1 Wilson and Jungner criteria applied to screening for RCC (adapted from [11]), highlighting key research questions

Criteria for screening	
1. The condition sought should be an important health problem	• Screening for RCC is a key research priority • RCC is the seventh most common cancer in Europe [25] and overall 5-year survival is 52%. • 20%–25% of patients have metastases at diagnosis and 5 year-survival in this group is 12%, suggesting early detection could improve survival.
2. There should be an accepted treatment for patients with recognised disease	• Early detection of smaller tumours may preferentially allow minimally invasive techniques, reducing rates of open surgery and therefore associated morbidity and length of hospital stay, and improving quality of life and renal function.
3. Facilities for diagnosis and treatment should be available	• Screening would increase disease incidence. Further research on cost and resource implications of this are key.
4. There should be a recognizable latent or early symptomatic stage	• The natural history of small renal masses is not completely understood. However, since >50% of RCCs are detected incidentally, this suggests there is a latent asymptomatic stage at which to intervene.
5. There should be a suitable test	• Currently, screening with ultrasound or low dose CT seems the most viable option. Ideally screening would adopt a staged approach to increase efficiency and cost-effectiveness. First a risk-stratification tool/prediction model would identify high-risk individuals from the general population. These individuals would be invited to have an initial urine or blood based biomarker test (ideally a point of care test at home or in the community), followed by further imaging in secondary care.
6. The test should be acceptable to the population	• Surveys demonstrate public acceptability and willingness to attend screening.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood	• This area is the highest research priority.
8. There should be an agreed policy on whom to treat as patients.	• Clear European Association of Urology guidelines on the management of RCC have been published [26], including active surveillance, ablative and surgical options for localised disease.
9. The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole	• A cost-effectiveness analysis of screening for RCC using ultrasound suggested that screening could potentially be cost-effective in men [27]. The low prevalence was a key determinant of cost-effectiveness, suggesting risk-stratified screening would be an ideal option.
10. Case finding should be a continuing process and not a “once and for all” project	• It is unclear if screening should be performed as a one-off or repeated at regular intervals.

Table 2 Potential screening tools

Tool	Advantages	Disadvantages
Ultrasound	– Non-invasive – Well tolerated – Relatively inexpensive – Widely available (most departments have ultrasound) – Does not involve ionizing radiation – Most well researched screening tool. A number of observational studies have been performed, however these collected only limited data, none were randomised, and all were published more than a decade ago [29–36]. – Potential for combination with the existing ultrasound-based abdominal aortic aneurysm screening program [36]. – Focused renal ultrasound has the advantage of imaging the kidney exclusively, therefore reducing the number of incidental findings in other abdominal organs. Conversely, imaging of the whole abdomen may identify other conditions, thus maximising benefit of screening.	– Operator dependent – Accuracy depends on lesion size: Detection of 85–100% tumours >3 cm in size, but only 67–82% of tumours 2-3 cm in size, therefore there is a potential for false negatives [37, 38]. – Dependent on anatomical factors such as obesity and presence of overlying bowel gas.
Low-dose non-contrast CT	– Most sensitive and specific of the proposed screening tools. – CT chest performed as part of lung cancer screening may be extended to include the kidneys. The Yorkshire kidney cancer screening trial, currently underway, is investigating the feasibility of this approach (ref: https://www.isrctn.com/ISRCTN18055040).	– Ionizing radiation – High cost and significant number of incidental findings suggest whole-body CT for the simultaneous detection of a number of conditions is unlikely to be cost-effective [39–41].
Urinary dipstick	– Non-invasive, quick, cheap – Can be performed in primary care with minimal training or at home by the patient themselves. – Can be used to screen for urological malignancies in combination. – In patients with non-visible haematuria, cancer detection rates are: 0%–16% for bladder cancer, 0%–3.5% for upper tract urothelial cancer and 0%–9.7% for RCC [42].	– Non-visible haematuria is a very common and non-specific finding, meaning screening using dipstick would generate a high volume of participants requiring further investigation, to detect only a very small number of RCCs [11]. – High number of false negatives as only 35% of individuals with RCC have visible or non-visible haematuria, compared to 94% in patients with urothelial carcinoma [43]. – A feasibility study of population screening utilising home urinary dipstick in 1747 men aged 50 to 75 years demonstrated that the prevalence of non-visible haematuria was 23%. However, only one RCC was detected and one RCC was missed [44].

(continued)

Table 2 (continued)

Tool	Advantages	Disadvantages
Plasma and urinary biomarkers	– Non-invasive – Perhaps the most promising biomarkers are: Urinary Aquaporin-1 and perilipin-2 [45] and plasma KIM-1 [46].	– A number of plasma and urinary biomarkers have been investigated including proteins [47], urinary exosomes and circulating tumour DNA (ctDNA), however none have been adopted into clinical practice.

main challenges associated with screening is the relatively low prevalence of RCC [29]; with prevalence being a major determinant of cost-effectiveness [27]. Targeted screening may overcome this, by identifying individuals at high risk, who would therefore benefit the most from screening, thus maximising efficiency [49]. A comprehensive systematic review of risk prediction models for RCC identified 11 models in which performance measures were reported; however only 6 models had been validated and only two had done so using external populations [50]. The majority of risk models incorporated a combination of demographic/lifestyle factors that are easily determined through medical records or self-assessment questionnaires, and/or biomarkers. Only one study considered genetic risk (e.g. single nucleotide polymorphisms). None of the biomarker risk factors were included in more than one study and a high risk of bias was noted, highlighting once again the challenges of biomarker research. Most of the models had acceptable-to-good discrimination (area under the receiver-operating curve >0.7) in development and validation. The risk factors that were included most commonly were: age, smoking status and BMI. One key challenge is that none of the risk factors for RCC are disease specific. Further external validation of risk prediction models is a priority.

Screening Implementation and Public Acceptability

The optimal frequency of screening for RCC is yet to be determined (e.g. one-off screening *vs* repeated screening at regular intervals). No studies have addressed this question thus far and insufficient evidence is known regarding the natural history and growth rates of undiagnosed disease to postulate regarding the value of repeated screening [11]. Once the optimal screening strategy has been identified, it will be crucial to determine whether the health care system has adequate resources to support implementation.

Although the general public have a relatively low awareness of RCC (82% knew nothing about RCC or had only heard of the condition), a high willingness to attend screening has been noted [48]. The vast majority of participants stated that they 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%; low-dose CT offered as part of lung screening: 95% [48]. Whether this translates to high attendance rates is unknown. Risk-stratified screening is viewed positively by the public.

Varying the starting age of RCC screening based on estimated risk from models incorporating phenotypic or genetic risk factors would be acceptable to most (83%) individuals, and is preferable to using sex alone. This may increase uptake, as 85% of participants reported they would be more likely to attend screening if the score suggested they were high-risk [51].

Current Nuances

As with any screening programme, potential harms include costs to the individual (both physical and psycho-social) and society (opportunity costs: monetary, resource allocation).

The ideal screening strategy would consist of a highly sensitive and specific test, which is non-invasive, cost-effective and well accepted by the population. A high test sensitivity is key to avoid missing cancers (false negatives) and falsely reassuring individuals with the disease and maintaining public confidence in the screening process.

A high specificity is crucial because screening large numbers of individuals (such as the whole population) may lead to a high number of people who require further investigations and potentially treatment, with subsequent risk of morbidity, anxiety and reduction in of quality of life. For example, even if the specificity of the test is 99%, screening a hypothetical cohort of 500,000 people/annum would lead to 5000 false positives/annum. There is a drive to reduce over-investigation and over-treatment of healthy individuals and to prevent over-medicalisation of the worried well [9]. This needs to be balanced against the relatively low prevalence of RCC, meaning that any potential harms would occur to detect only a small number of individuals with cancer. Two systematic reviews and meta-analyses have been performed evaluating the prevalence of undiagnosed RCC in asymptomatic individuals undergoing screening with ultrasound and CT respectively. The pooled prevalence was 0.21% (95% CI, 0.14–0.28%) in a North American cohort undergoing CT and 0.17% (95% CI 0.09–0.27%) in a European and North American cohort undergoing ultrasound [29, 52]. This suggests screening 1000 individuals would lead to the detection of between 1 and 3 cancers; thus screening our hypothetical cohort of 500,000 individuals would detect up to 1500 cases of RCC. As already mentioned, risk-stratified screening may help overcome this challenge.

A unique screening consideration is linked to our current understanding of the natural history of RCC and our ability to accurately determine diagnosis and prognosis. Unlike other malignancies that have an existing screening program, RCC does not have an identifiable pre-malignant state (such as carcinoma in situ in the breast, cervical intraepithelial neoplasia and adenomatous polyps of the colon). It is postulated that all RCCs must start off as small renal masses (SRM), and genomic studies suggest copy number aberrations affecting the VHL pathway occur as early as adolescence [53]. However, once a SRM is detected, there are difficulties in differentiating malignant from benign disease (especially fat poor angiomyolipoma

and oncocytoma) despite imaging and renal biopsy, meaning 20% of SRM treated surgically are found of be benign post-operatively [54]. More recent studies suggest this may be as high as 30% [55].

In addition to diagnostic challenges relating to SRM, there are also complexities relating to patient risk stratification and prognosis. 30% of SRM display aggressive growth (rapid growth or doubling time < 12 months), whilst the remainder grow slowly or remain stable [56, 57]. 3–12% of SRM will either present with concurrent metastases or will develop metastases at a later date [58], however there is a lack of validated scores for risk stratification. Linear growth rate has been proposed as a marker for aggressiveness, but this has recently been challenged, as it did not correlate with overall outcomes, and similar average growth rates were observed for benign and malignant (low and high grade) SRM [59, 60].

As such, a potential consequence of screening is the over-diagnosis of SRM with indolent potential which would not have otherwise affected patient survival. In screening, lead time bias refers to an artificially inflated survival time noted simply through earlier diagnosis of a cancer rather than truly affecting mortality. Length time bias refers to artificially inflated survival time noted in screening secondary to the detection of indolent and therefore slow growing disease (relative to aggressive disease which is more likely to be detected by the symptomatic patient pathway) [8]. RCCs detected incidentally have a lower grade and stage and better survival than cancers detected due to symptoms [61]. Our understanding of the natural history of the disease has improved in recent years thanks to increasing use of diagnostic biopsies, patient registries and trials of active surveillance. Improvements in imaging (such as contrast enhanced ultrasound and MRI) as well as more nuanced treatment strategies (use of active surveillance, ablation and nephron sparing surgery) aim to reduce over-treatment and offer risk-based management. In addition, it is crucial to determine if screening would lead to an increase in the detection of RCC beyond that already noted due to the increased use of abdominal imaging. 43% of individuals aged 65–85 years on Medicare in the USA undergo either a CT chest or CT abdomen over a 5-year period [5], although the numbers are likely to be lower in non-privatised healthcare systems. Ultimately, a RCT would enable us to tease out if screening would lead to a stage shift and if this would impact survival.

Depending on the screening tool used (focused renal ultrasound vs imaging of the whole abdomen), incidental findings will be identified. Although some of these will have uncertain clinical significance and may lead to increased investigations and worry/anxiety, this could be balanced by the added benefit from the identification of other abdominal malignancies or potentially life-threatening benign disease (e.g. aortic aneurysms). No studies have been performed to investigate the potential impact of screening for RCC itself on participants' quality of life [29], although studies in other conditions suggest that the impact of screening is either negligible or short lived (Aneurysms [62], breast [63] and ovarian cancer [64, 65]).

Key Points

- The incidence of RCC is highest in the developing world and rates are rising – partially due to increases in risk factors, but also secondary to incidental detection during abdominal imaging for other conditions
- The main risk factors for RCC are: advancing age, male sex, obesity, hypertension and smoking
- Screening for RCC has been identified as a top research priority by clinicians, researchers and the public.
- It is postulated that screening for RCC may improve survival outcomes through earlier detection, however the ideal screening modality and screening population have yet to be elucidated. No RCT of screening for RCC have been performed.
- The most likely potential screening tools would be imaging-based, with either ultrasound or low-dose CT (potentially in combination with other screening programs). Although promising, no blood or urine biomarkers have been approved for clinical use.
- The relatively low prevalence of RCC limits cost-effectiveness. Risk-stratified screening may overcome this, however established risk factors for RCC are not disease specific, limiting accuracy.
- Screening for RCC is acceptable to the public and there is public appetite for a screening study.
- Important screening considerations include: risk of overdiagnosis, management of incidental findings, nuances associated with limited understanding of the natural history of small renal masses.

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