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Meta-analysis of the prevalence of renal cancer detected by abdominal ultrasonography

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Key words: Renal cell carcinoma, renal mass, screening, ultrasonography, meta-analysis.

Abstract

Introduction: The potential for an ultrasound based screening programme for renal cell carcinoma (RCC) to improve survival through early detection has been the subject of much debate. The prevalence of ultrasound detected asymptomatic RCC is an important first step to establishing whether a screening programme may be feasible.

Methods: A systematic search of Medline and Embase was performed until March 2016 to identify studies reporting the prevalence of renal masses and RCC. Two populations of patients were chosen, asymptomatic individuals undergoing screening ultrasonography and patients undergoing ultrasound for abdominal symptoms not related to RCC. A random effects meta-analysis was performed. Study quality was evaluated using a validated 8-point checklist.

Results: Sixteen studies (n=414 266) were included in the final analysis. The pooled prevalence of renal masses was 0.36% (95% CI 0.23-0.52%) and the prevalence of histology-proven RCC was 0.10% (95% CI 0.06-0.15%). The prevalence of RCC was more than double in studies from Europe and North America compared to Asia (0.17% (0.09-0.27%) *vs* 0.06% (0.03-0.09%)). Data on 205 screen-detected RCCs demonstrated that 84.5% of tumours were stage T1-T2, 13.5% were T3-T4, and only 2% had positive nodes or metastases at diagnosis.

Conclusion: At least one renal cell carcinoma would be detected per 1 000 individuals screened. The majority of tumours identified are early stage (T1-T2).

Introduction

Overall survival from renal cell carcinoma (RCC) is poor, with a 47% five-year age standardized relative survival rate in the United Kingdom [1]. Half of all patients with renal cancer present with asymptomatic disease and therefore many cancers are detected late, with over a quarter of individuals diagnosed with RCC having evidence of metastases at presentation [2, 3]. Patients with metastases have a 6% five-year (age standardized relative) survival rate compared to 84% survival in patients with stage one disease [1]. Incidentally detected tumours are generally smaller in size and are associated with improved survival relative to symptomatic tumours, independent of tumour grade and stage [4, 5]. A screening programme consisting of abdominal ultrasound, potentially in a selected higher risk population, in theory could improve survival outcomes through early detection and treatment of RCC. Previously, the low prevalence of renal cancer in the general population and relatively poorly understood natural history of renal masses were considered major barriers to establishing a cost effective screening service [6]. More recently, there has been a resurgence in interest in a screening programme for RCC [7]. The established abdominal aortic aneurysm (AAA) screening programme in men over the age of 65 years in the United Kingdom represents an ideal model to explore the possibility of screening for RCC due to the similarities in risk factors and mode of detection between RCC and AAA [8]. Furthermore, it has been postulated that early detection of asymptomatic RCC through a targeted national screening programme may potentially downstage the disease, reducing the prevalence of metastatic tumours and associated expenditure relating to systemic therapies. Although a number of drugs for the treatment of mRCC are available they are very expensive [9-11].

Prior to consideration of a screening study for RCC it is essential to assess potential cost effectiveness, by assembling all relevant evidence on the incremental costs and consequences of screening into an economic model. One of the key parameters that will inform cost-effectiveness is

the prevalence of renal masses and RCC in a screened population [12]; therefore, in this study, a systematic review and meta-analysis was performed to determine RCC prevalence.

Methods

Data sources and search strategy

The study protocol was registered on the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO/ ; CRD42016036899) and the study conducted in accordance with PRISMA guidelines (Table S1). A systematic literature search was performed in Medline (January 1976-March 2016) and Embase (January 1976-March 2016) databases. Full details of the keywords and subject headings used are available in supplemental table S2. The reference list of all relevant articles was manually reviewed.

Inclusion and exclusion criteria

Study inclusion, data extraction and data quality assessments were performed independently by two reviewers (SHR and RH), with discrepancies resolved by a third investigator (GDS). Full inclusion and exclusion criteria are reported in Table S3. Studies were included in the analysis if the prevalence of renal masses and/or RCC was reported in asymptomatic individuals undergoing abdominal ultrasound ("screening" group), patients undergoing abdominal ultrasound for a medical reason not related to RCC ("incidental finding" group) or the study comprised a combination of both screened as well as non-screened individuals ("mixed" group). Studies were excluded if ultrasound was performed in individuals that did not represent a general adult population or if patients had symptoms of renal cancer (flank pain, abdominal mass, non-visible and/or visible haematuria). Patients undergoing ultrasound for suspected renal colic were also excluded as symptoms may have been secondary to RCC rather than renal stones. Studies which performed ultrasound screening in individuals with familial syndromes predisposing to RCC or patients with renal transplant or end stage renal disease were also excluded from the analysis.

Study Quality Assessment

A validated checklist was utilized to assess the quality of studies reporting the prevalence of renal masses in a screening population, with studies scored out of a total of 8 points [13]. Item 6 on the checklist evaluates whether the studies reported the participation rate of individuals invited to attend screening. Studies reporting the prevalence of incidental renal masses in patients undergoing ultrasonography for a non-urological complaint were assessed on a modified 7-point checklist, as Item 6 was no longer a valid item in this group. Item 3 on the checklist evaluates whether the study sample size was sufficient to estimate prevalence with an adequate level of confidence and precision. Studies were awarded a point if they included more than 5 107 participants (sample size calculation appendix 1). Study quality was used to perform subgroup analysis. No studies were excluded from the meta-analysis based on quality score or sample size.

Study outcomes

The primary study outcomes were the prevalence of solid or complex cystic renal masses suspicious for RCC on ultrasound and the prevalence and stage distribution of histology-proven RCC in asymptomatic individuals. The secondary outcome was the prevalence of other renal and adrenal pathology. Pre-planned subgroup analysis consisted of study type (i.e. screening, mixed or incidental finding), study geographical region of origin, publication year and study quality. The prevalence of RCC by established risk factors such as age, gender, hypertension, smoking and body mass index (BMI) was assessed.

Statistical analysis

The statistical analysis was performed using Stata version 12.0 (Stata Corp, College Station, TX). The meta-analysis was performed on the double arcsine transformation (appendix 2) for each proportion, using the generic inverse variance method. The double arcsine transformation stabilizes the variance and is particularly useful for proportions which are at the extremes of the 0 to 1 range,

as is the case for an uncommon condition such as RCC [14]. In this case, asymmetrical confidence intervals are created to avoid reporting a prevalence in the negative range. As such, it is not appropriate to use funnel plots to assess for publication bias, as the typical funnel shape relies on symmetry of confidence intervals. Heterogeneity was assessed using the chi-square test and the I-squared (Cochran's Q) statistic. The pooled prevalence was calculated using a random-effects model due to significant study heterogeneity. Meta-regression was used to assess the association between study characteristics (including study type, size, publication year and geographical region) and the prevalence of RCC. A p value of < 0.05 was reported as statistically significant.

Results

Data retrieval and study quality

Following exclusion of duplicates, the search yielded 2658 articles. Sixteen studies were included in the final meta-analysis for renal masses (n=414 266 individuals) (Figure 1 and Table 1). The median quality score for studies in the screening and mixed groups was 4 (range 3-6) out of a potential 8 points, whereas studies in the non-screening group only achieved a median score of 1.5 (range 1-3) out of a potential 7 points (Table S4). All studies were observational in nature, consisting of one study arm alone (i.e. no non-screening comparator), and none utilised a random sampling method. Only one study commented on the participation rate of individuals invited to attend screening [15]. None of the studies reported 95% confidence intervals (CI) for point estimates of prevalence, despite the fact that this was an item on the quality assessment checklist (although this is readily calculable, given knowledge of the sample size). Three studies did not clearly state ultrasound criteria used to define a suspicious renal mass and three further studies only included solid (rather than complex cystic) masses in this definition. Five studies reported data on the prevalence of renal masses, but no histological data was available, therefore these studies were excluded from the analysis of the prevalence of histology-proven RCC. All studies reporting the prevalence of histology-proven RCC were based on operative (rather than biopsy) specimens.

Primary outcomes

The pooled prevalence of renal masses was 0.36% (95% CI 0.23-0.52%; (Figure 2). The pooled prevalence of histology-proven RCC was 0.10% (95% CI 0.06-0.15%; Figure 3). Significant study heterogeneity was noted for both outcomes (Chi^2 327.60, d.f.=15, p<0.00001, I^2 96% and Chi^2 112.62, d.f.=11, p<0.00001, I^2 91%). Out of the 10 studies investigating the prevalence of screen-detected RCC, a wide variability in the method used for reporting the size and stage of the tumours was noted. Only 3 studies reported data on the TNM staging of the detected RCCs [8, 15, 16], with two of these using TNM 1992 classification and one using TNM 1997. Two studies reported staging by

Robson's classification [17, 18] and three studies reported individual tumour size but not tumour stage [19-21]. Differences in reporting of data limited the ability to pool results on the size and stage of screen-detected RCC, and therefore three different grouping methods were used (Table S5). Data on 66 cancers from four studies were pooled to reveal that 45% of screen detected cancers were ≤4cm, 41% RCCs were between 4 and 7cm, with only 14% over 7cm in size [8, 15, 21]. Similarly, data on 185 screen detected RCCs from two further studies demonstrated 80% of tumours were less than 5cm in size [16, 20]. In addition, pooling data on 205 screen-detected RCCs from three studies showed that 84.5% of tumours were stage T1 or T2, 13.5% RCC were T3-T4N0, and only 2% had positive lymph nodes or metastases at diagnosis (TNM 1992 classification) [8, 15, 16].

Secondary outcomes

A number of additional renal and adrenal pathologies were identified among the studies (Table S6). Of note, Mihara et al reported detection of an additional 5 (prevalence 0.0023%) malignant, non-RCC kidney lesions in addition to the cases of RCC (prevalence 0.086%) [16]. Due to heterogeneity of reported data, only the prevalence of asymptomatic hydronephrosis and renal stones were pooled in a meta-analysis (Supplemental figure S1 and S2). The pooled prevalence of hydronephrosis was 0.48% (95% CI 0.21-0.87%, Chi^2 = 76.75, df= 5, p<0.00001, I^2 =95%) and the prevalence of asymptomatic renal stones was 1.8% (95% CI 0.59-3.6%, Chi^2 = 844.78, df= 9, p<0.00001, I^2 =100%).

Subgroup analysis

The geographical region in which the study was undertaken was the only subgroup that consistently affected the prevalence of renal masses and histology proven RCC (Table 2). However, assessing the prevalence by study geographical region did not reduce heterogeneity. The prevalence of renal masses and RCC was more than double in studies from Europe and North America compared

to studies from Asia (renal mass: 0.70% (95% CI 0.31-1.22%) *vs* 0.30% (95% CI 0.14-0.52%); RCC 0.17% (95% CI 0.09-0.27%) *vs* 0.06% (95% CI 0.03-0.09%)). Geographical region was a significant determinant of the prevalence of RCC in meta-regression (p=0.002) but notably study type and quality were not (p=0.876 and p=0.432 respectively; Table S7). The effect of publication year, study type and study quality was not consistent across the two outcomes. The pooled prevalence of renal masses was higher in the non-screening subgroup compared to the screening subgroup (0.73% (95% CI 0.31-1.3%) *vs* 0.25% (95% CI 0.17-0.35%)); however, this pattern was not noted in terms of the prevalence of RCC, with lower prevalence of cancer in the non-screening compared to the screening subgroup (0.05% (95% CI 0.00-0.16%) *vs* 0.11% (95% CI 0.06-0.17%)).There was insufficient data to assess the impact of established risk factors for the development of RCC, i.e. patient age, hypertension, smoking status and BMI on the prevalence of cancer. Only five studies reported sufficient data to allow a calculation of the prevalence of RCC by gender [8, 15, 19, 20, 22]. The pooled prevalence of RCC was higher in men compared to women (0.09% (95% CI 0.03-0.18%) *vs* 0.01% (95% CI 0-0.05%)).

Discussion

Early detection and screening for cancer has been identified as a key priority for the National Health Service, with increased resource allocation and media coverage [23]. Though the UK National Screening Committee has released recommendations regarding screening for colorectal, breast, prostate, ovarian and lung cancer, screening for RCC has yet to be discussed as there is currently incomplete data, with relatively little research published in the literature over the last decade [2, 24]. Data on the prevalence of RCC in asymptomatic individuals undergoing abdominal ultrasonography is lacking, but is essential to inform an economic evaluation of the cost effectiveness of an ultrasound based screening programme. Here a pooled prevalence of renal masses of 0.36% (95% CI 0.23-0.52%) with a pooled prevalence of histology-proven RCC of 0.10% (95% CI 0.06-0.15%) was demonstrated. Current National Cancer Intelligence Network data suggest that although 44% of patients diagnosed with RCC are stage 1 at presentation, only 10% are stage 2, with over 25% having metastases [25]. The meta-analysis showed that 84.5% of screen-detected tumours were stage T1 or T2, 13.5% were T3, and only 2% had positive nodes or metastases at diagnosis, suggesting a potential favourable stage shift in screen-detected disease.

It is anticipated that focused screening renal ultrasonography will lead to detection of other benign and malignant renal and adrenal abnormalities. The prevalence of screen-detected hydronephrosis was estimated to be 0.48% (95% CI 0.21-0.87%) and renal stones 1.8% (95% CI 0.59-3.6%). Unfortunately, there was insufficient data to estimate the pooled prevalence of benign masses of the renal fossa, such as angiomyolipoma and oncocytoma, nor the prevalence of renal cysts, the most common screen-detected renal pathology. The prevalence of asymptomatic cysts is estimated to be 30% in individuals aged >70 years [26]. A proportion of screen-detected cysts may require further imaging, discussion with a specialist and potentially treatment. An evaluation of a screening programme for RCC must take into consideration the impact of incidentally detected

benign renal lesions on patients and health services. There is a potential for false positive results and over-diagnosis of slow-growing small renal masses (SRM). Currently, 15-30% of SRM are found to be benign following surgical excision [27-29]. Advances in the determination of the aetiology of SRMs, with increased utilization and better interpretation of renal biopsy, may reduce these rates in future [30]. Up to one third of small renal cancers exhibit aggressive potential (rapid growth or doubling time <12 months), with the remainder growing slowly or remaining stable in size[31, 32]. It is anticipated that in future, the development of non-invasive modalities, such as urinary biomarkers, will allow improved discrimination between benign and malignant SRM (with further differentiation between indolent and aggressive RCC), enabling personalised treatment strategies and reducing over-treatment [33].These considerations may be further offset by the potential benefit derived from early detection of other malignancies within the renal fossa (including adrenal and upper urinary tract urothelial cell cancers, renal secondary metastases, renal carcinoid, sarcoma and lymphoma). Spouge et al reported the prevalence of these combined malignancies as 0.2%, whereas Mizuma et al, Malaeb et al and Patel et al all reported a prevalence of 0.03% [8, 19, 34]. These rates vary considerably and unfortunately insufficient data was available to complete a meta-analysis. Further studies are needed to quantify this and to estimate the potential impact on health services.

It is likely that this meta-analysis underestimated the true prevalence of histology-proven RCC. Several studies reported a higher prevalence of suspected RCC, however due to patient loss to follow up or contra-indications to surgery, histological confirmation was only available in a portion of these [8, 15, 16, 20]. For example, Malaeb et al screened 6 678 individuals with ultrasound and confirmatory CT demonstrated 22 solid renal masses suspicious for RCC, however histology was only available in 15 of these cases (68%), potentially underestimating the true prevalence of malignancy [8]. Furthermore, only half of the studies included in the meta-analysis represented a European or North American population, with the remainder of studies originating from Asia or the Middle East. Our

results suggest that there is significant variability between the prevalence of screen-detected RCC in different geographical areas, in keeping with known epidemiological data [35]. The prevalence of RCC in studies originating from Europe and North America (0.17%; 95% CI 0.09-0.27%) was more than double the prevalence in Asia (0.06%; 95% CI 0.03-0.09%). Another factor that may have contributed to a potential underestimation of the true prevalence of RCC is the young age of the screening study participants. Only 1 out of 8 screening studies reported a participant mean age over 65 years and 5 out of 8 studies included individuals under the age of 30 years. Young patients with RCC are at greater risk of familial syndromes predisposing to cancer, however due to lack of patient level data, it was not possible to exclude young participants by age from the analysis. In addition, the included studies were published between 1982 and 2010, with over 80% (13 out of 16) published prior to 2006. Such factors restrict the applicability of these results to the population of interest in the United Kingdom, and highlight the need for more high quality research in a contemporary Western population. Obesity and older age are established risk factors for the development of RCC [36, 37], and with the rising obesity epidemic and aging population, the incidence of RCC is expected to rise in future.

This meta-analysis included relatively low quality studies. The retrospective design and substantial rates of loss to follow-up should all be taken into consideration when interpreting the results. In addition, there were discrepancies in the ultrasound criteria used to define a renal mass in different studies. Importantly, none of the studies compared a screening intervention to a non-screening group or used a random sampling method to select study participants. In addition, methods utilised by the studies to recruit participants may also introduce bias within the “screening group.” For example, two studies offered abdominal ultrasound to asymptomatic individuals as part of an employee health check-up, rather than screening individuals through a population registry. The inclusion of studies assessing the prevalence of renal cancer in patients undergoing abdominal ultrasound for a medical reason not related to kidney cancer (“incidental finding” group) may have

introduced heterogeneity in the data. These smaller studies are also more prone to potential publication bias. However, neither study type nor study quality score were found to be significant factors in meta-regression and further, heterogeneity remained high even when pooling only screening population studies. The persistent heterogeneity may in part be attributed to differences in study design and patient populations. The included studies reported only limited data on the prevalence of renal cancer by established risk factors, precluding any formal analysis. Though, as expected, the prevalence of RCC was found to be higher in males compared to females, it is likely that due to small sample sizes the estimate of effect size is inaccurate, hindering conclusions regarding the potential for targeted screening.

The results of this meta-analysis on the prevalence of RCC detected by ultrasound is broadly in keeping with what would be expected from the data published for screening non-contrast CT. Two studies have attempted to pool data from the literature to quantify the prevalence of renal cancer in asymptomatic individuals, and both of these utilised non-contrast CT rather than ultrasound as a screening tool. Fenton et al calculated the pooled prevalence of renal cancer in asymptomatic American patients undergoing non-contrast screening CT as 0.21% (95% CI 0.14-0.28%) [38]. Wernli et al estimated the pooled prevalence of renal masses as 0.22% in patients undergoing non-contrast CT colonography; with a rate of 0.06% in screened populations and 0.42% in non-screening populations [39]. Conversely, ultrasound is known to be less sensitive and specific compared to non-contrast CT for the detection of renal cancers; with ultrasound detection rates being dependent on renal lesion size, a factor that would need to be considered in the design of a screening programme in terms of frequency of ultrasound scanning [40]. Studies examining autopsies or cadaveric organ donors estimate a prevalence of RCC of 0.7% to 0.9% (mean age of study participants: 65 years) [41, 42]. This is substantially higher than the prevalence suggested by the meta-analysis, raising once again the possibility that the true prevalence of histology-proven RCC may have been under-estimated.

This meta-analysis suggests that screening 1 000 individuals would result in 4 patients undergoing further imaging of a renal mass, and that at least 1 of these patients would be diagnosed with RCC. The clinical significance of these findings is best appreciated in the context of other established screening programmes (Figure 4). The UK AAA screening programme identifies 10 men with an AAA >3cm for every 1 000 individuals screened. However, only 2 men receive elective surgery to repair a large AAA following initial screening [43]. An additional 6 individuals require elective surgery to repair a large AAA following active surveillance over a twenty year period [44]. Results from the Bowel Cancer Screening Programme in England demonstrate that 1.6 colorectal cancers are detected for every 1 000 individuals screened using guaiac-based faecal occult blood tests. An additional 6 cases are detected with high risk adenomatous polyp requiring surveillance colonoscopy[45]. The UK Breast Cancer screening programme detection rate is 8.3 per 1 000 women screened [46]. This number is much higher than the projected values for RCC screening, however it is estimated that 15% to 25% of screen-detected breast cancers consist of over-diagnosis [47]. Screening for RCC may compare favourably to the established programmes for AAA and colorectal cancer, although intrinsic differences underlying each screening programme and the individual nature of each disease make direct comparisons artificial.

In isolation, this meta-analysis is insufficient to support or refute a screening programme for RCC and should not replace a full consideration of the Wilson-Jungner criteria [49]. A cost effectiveness analysis is beyond the scope of this paper, but should constitute an essential next step towards establishing the potential value of screening.

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Figure legends

Figure 1: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram demonstrating study search strategy.

Figure 2: Forest plot demonstrating the pooled prevalence of suspicious renal masses detected by ultrasonography, generated by a random effects meta-analysis. Results are shown in three subgroups: screening population, incidental finding and mixed. Study author, year, the number of renal masses (n) and the total number of study participants (N) are shown. Prevalence (n/N) is demonstrated as a percentage, labelled as ES (effect size) along with 95% confidence intervals (CI).

Figure 3: Forest plot demonstrating the pooled prevalence of histology-proven RCC (renal cell carcinoma) detected by ultrasonography, generated by a random effects meta-analysis. Results are shown in three subgroups: screening population, incidental finding and mixed. Study author, year, the number of renal cancers (n) and the total number of study participants (N) are shown. Prevalence (n/N) is demonstrated as a percentage, labelled as ES (effect size) along with 95% confidence intervals (CI).

Figure 4: Infographic delineating comparative detecting ability of established UK screening programs versus screening for renal cell carcinoma. Our meta-analysis suggests screening 1 000 individuals would detect at least 1 renal cell carcinoma (green). Screening 1 000 individuals detects 1.6 colorectal cancers (blue), 8 breast cancers (pink) and 10 abdominal aortic aneurysms ≥ 3cm (red).

Table legends

Table 1: Characteristics of included studies

Table 2: Subgroup analysis for the pooled prevalence of renal masses and histology-proven renal cell carcinoma (RCC)

Figure legends: Supplementary figures

Figure S1: Forest plot demonstrating the pooled prevalence of hydronephrosis detected by ultrasonography, generated by a random effects meta-analysis. Results are shown in two subgroups: screening population and incidental finding. Study author, year, the number of cases of hydronephrosis (n) and the total number of study participants (N) are shown. Prevalence (n/N) is demonstrated as a percentage, labelled as ES (effect size) along with 95% confidence intervals (CI).

Figure S2: Forest plot demonstrating the pooled prevalence of renal stones detected by ultrasonography, generated by a random effects meta-analysis. Results are shown in two subgroups: screening population and incidental finding. Study author, year, the number of cases of renal stones (n) and the total number of study participants (N) are shown. Prevalence (n/N) is demonstrated as a percentage, labelled as ES (effect size) along with 95% confidence intervals (CI).

Table legends: Supplementary tables

Supplementary Table S1: Completed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist

Supplementary Table S2: This table illustrates the review search strategy. Medline and Embase were searched, using the Ovid platform. Key words and Medical Subject Headings (MeSH) used are shown,

where $ indicates right-hand truncation (i.e., search for variations on a word that are formed with different suffixes) and ? is used to retrieve words with both British and American spelling variations. All searches were limited to humans and publications in the English language.

Supplementary Table S3: Details of inclusion and exclusion criteria

Supplementary Table S4: Assessment of methodological quality diagram, based on a validated 8-point checklist described by Loney et al[13]. Green indicates that the study fulfilled the item on the checklist, whereas red indicates that the item was not met. Items are left blank when not relevant to the study type.

Supplementary Table S5: Size and stage distribution of screen-detected renal cell carcinomas

Supplementary Table S6: Prevalence of renal and adrenal pathology

Supplementary Table S7: Meta-regression for prevalence of histology-proven renal cell carcinoma

Table 1

Study (year)	Country	Data collection dates	Sample size	Sample Recruitment	Sample Demographics: Mean or median age (range), % male
Fujii (1995)[22]	Japan	April 1985-March 1991	17941	Asymptomatic individuals, Employee health check-up	Median 53 years (21-85), 72% male.
Spouge (1996)[18]	Canada	6-month period, not specified	1,000	Asymptomatic individuals, Employee health check-up for business executives	Mean 46.2years (29-63), 91% male
Spouge (1996)[18] 2nd sample	Canada	2.5-year period, not specified	7,925	Asymptomatic individuals, Employee health check-up for business executives	Not reported
Mihara (1999)[16]	Japan	August 1983-March 1996	219,640	Asymptomatic screening of general population	Age range 29-70 years, Gender not reported
Tsuboi (2000)[20]	Japan	January 1993-June 1997	60,604	Asymptomatic individuals, health check-up for the general population	Age range 15-96, 67% male.
Mizuma (2002)[19]	Japan	February 1990-December 1995	16,024	Asymptomatic individuals, health check-up for the general population	Mean 47 years (25–84 years), 58% male.
Filipas (2003)[15]	Germany	December 1996 for 13 months and January 1998 for 13 months	9,959	Asymptomatic screening of general population, individuals aged >40 years	Mean 61 years (40-94 years), 49% male
Malaeb (2004)[8]	USA	1993-1997	6,678	Asymptomatic screening of veterans (in conjunction with AAA screen)	Mean 66.2 years (50-79 years), 97% male
Mosharafa (2007)[50]	Eight Middle Eastern countries	January 2005-December 2005	8,551	Asymptomatic individuals, health check-up for the general population	Mean age 43.5 years (SD 13.9), 70% male
Tosaka (1990)[17]	Japan	1982-1988	41,364 (20,897 screening+ 20,467 non-screening)	Mixed: asymptomatic individuals (part of health check-up) and patients undergoing abdominal ultrasound for non-urological complaint	Not reported
Haliloglu (2010)[21]	Turkey	March 1995-February 2008	18,203	Mixed: asymptomatic individuals (part of health check-up) and patients having ultrasound for LUTS	55 years (33-90 years), 64% male.
Fields (1985)[51]	USA	Not reported	500	Abdominal ultrasound for non-urological complaint	Not reported
Bodner (1990)[52]	USA	Not reported	86	Spinal cord injury patients, no urological symptoms	Mean 41.7 years, 99% male
Al-Durazi (2003)[53]	Bahrain	January 2001-December 2001	100	Men with acute retention secondary to BPH	Mean 67 years (54-96), 100% male
Belani (2004)[54]	USA	3 months, not specified	600	Abdominal ultrasound for non-urological complaint	Mean 53 years (18-95), 32% male
Heikkinen (2005)[55]	Finland	January 1993-January 1994	400	Patients undergoing investigations for dyspepsia	Mean 55.8 years (ENG), mean 58.3 years (EPG), 38% male.
Patel (2009)[34]	UK	April 1994-February 2007	3,976	Men with LUTS	65 years (15-91), 100% male

Abbreviations for table 1: AAA= abdominal aortic aneurysm; BPH= benign prostatic hyperplasia; ENG= Endoscopy negative group; EPG= Endoscopy positive group; LUTS= lower urinary tract symptoms; RCC= Renal cell carcinoma; UK = United Kingdom; USA= United States of America.

Table 2

Subgroup	Prevalence of renal masses (95% CI)	Prevalence of histology-proven RCC (95% CI)
Overall pooled prevalence	0.36% (0.23-0.52)	0.10% (0.06-0.15%)
Study publication year		
Prior to the year 1999:	0.67% (0.31-1.1%)	0.11% (0.06-0.18%)
Between 2000 and 2004:	0.17% (0.07-0.30%)	0.08% (0.02-0.17%)
After the year 2005:	0.32% (0.10-0.67%)	0.12% (0.04-0.23%)
Study quality		
Studies with quality score ≥4:	0.28% (0.19-0.395)	0.12% (0.07-0.18%)
Studies with quality score <4:	0.55% (0.22-0.99%)	0.03% (0- 0.09%)
Geographical region		
Asia	0.30% (0.14-0.52%)	0.06% (0.03-0.09%)
Europe and North America:	0.70% (0.31-1.22%)	0.17% (0.09-0.27%)
Middle East	0.16% (0-0.66%)	0.20% (0.14-0.27%)

Appendices

Appendix 1: Sample size calculation for study quality assessment

The following formula was utilized to calculate the adequate sample size (N) for prevalence studies, as previously described [56]:

$$N = Z^2 P (1-P) (1/d^2)$$

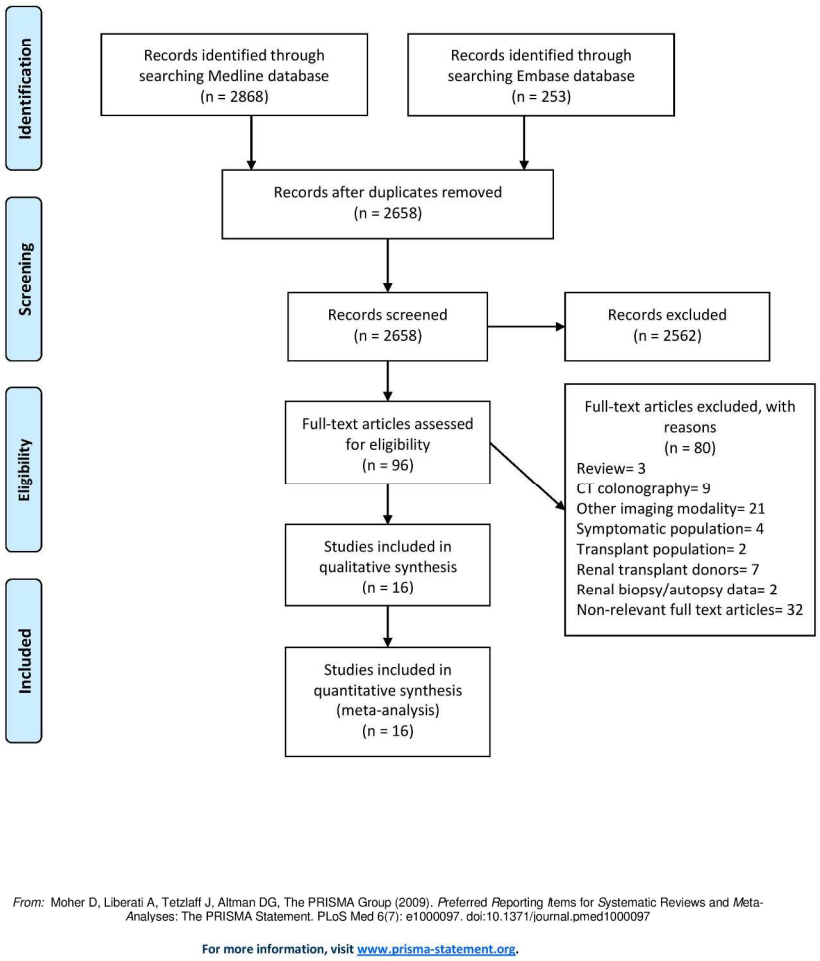
Where P is the estimated prevalence of renal masses of 0.3% [16] and Z is the statistic corresponding to a 95% confidence level. A less conservative definition of precision (d) was used due to the low prevalence, where d is equal to the prevalence divided by 2 .

Appendix 2: The Freeman-Tukey double arcsine transformation[14]

The double arcsine transformation (t) is derived using the following formula, where *n* is the number affected and *N* is total sample size and *Var* is the variance.

$$t = \sin^{-1}\sqrt{\frac{n}{N+1}} + \sin^{-1}\sqrt{\frac{n+1}{N+1}} \qquad \mathrm{Var}(t) = \frac{1}{N+0.5}$$

Figure 1



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 1: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram demonstrating study search strategy.

215x279mm (300 x 300 DPI)

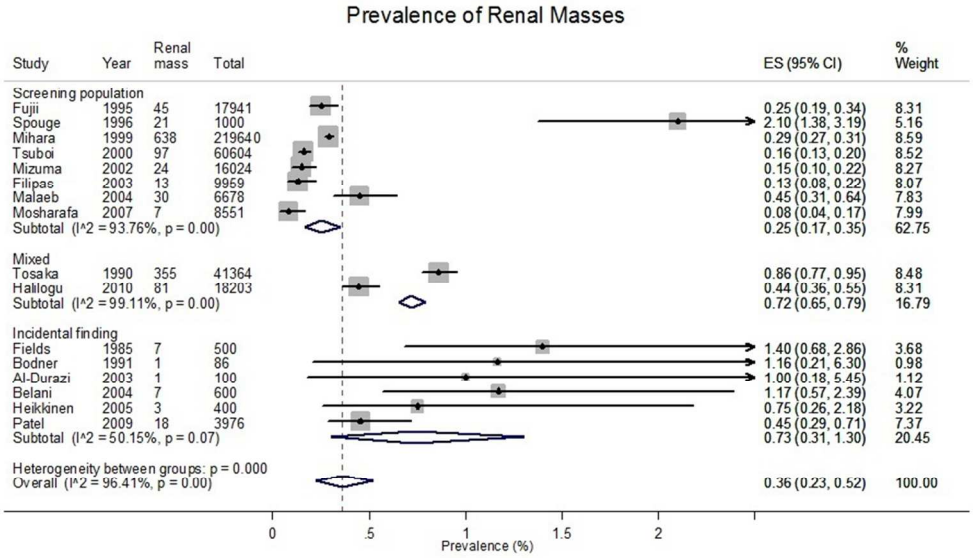


Figure 2: Forest plot demonstrating the pooled prevalence of suspicious renal masses detected by ultrasonography, generated by a random effects meta-analysis. Results are shown in three subgroups: screening population, incidental finding and mixed. Study author, year, the number of renal masses (n) and the total number of study participants (N) are shown. Prevalence (n/N) is demonstrated as a percentage, labelled as ES (effect size) along with 95% confidence intervals (CI).

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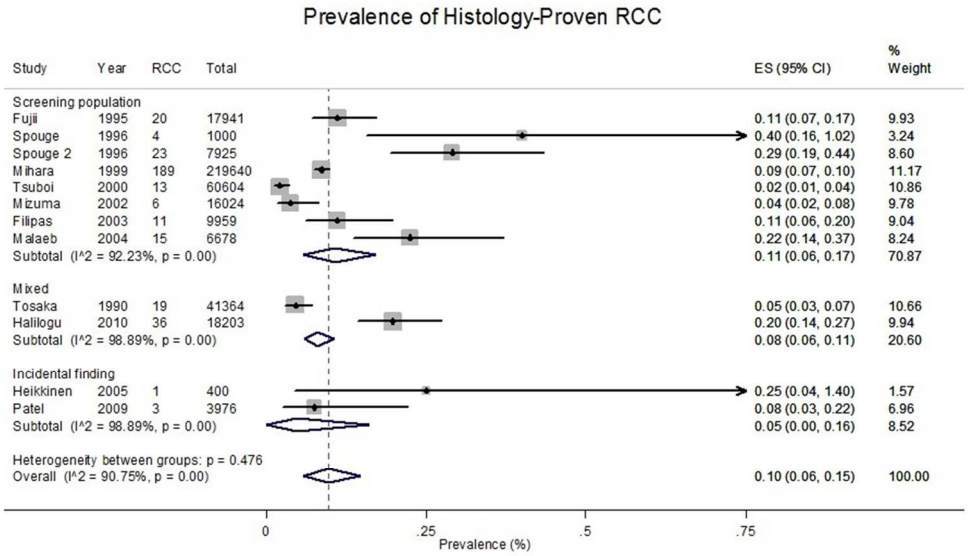

Figure 3: Forest plot demonstrating the pooled prevalence of histology-proven RCC (renal cell carcinoma) detected by ultrasonography, generated by a random effects meta-analysis. Results are shown in three subgroups: screening population, incidental finding and mixed. Study author, year, the number of renal cancers (n) and the total number of study participants (N) are shown. Prevalence (n/N) is demonstrated as a percentage, labelled as ES (effect size) along with 95% confidence intervals (CI).

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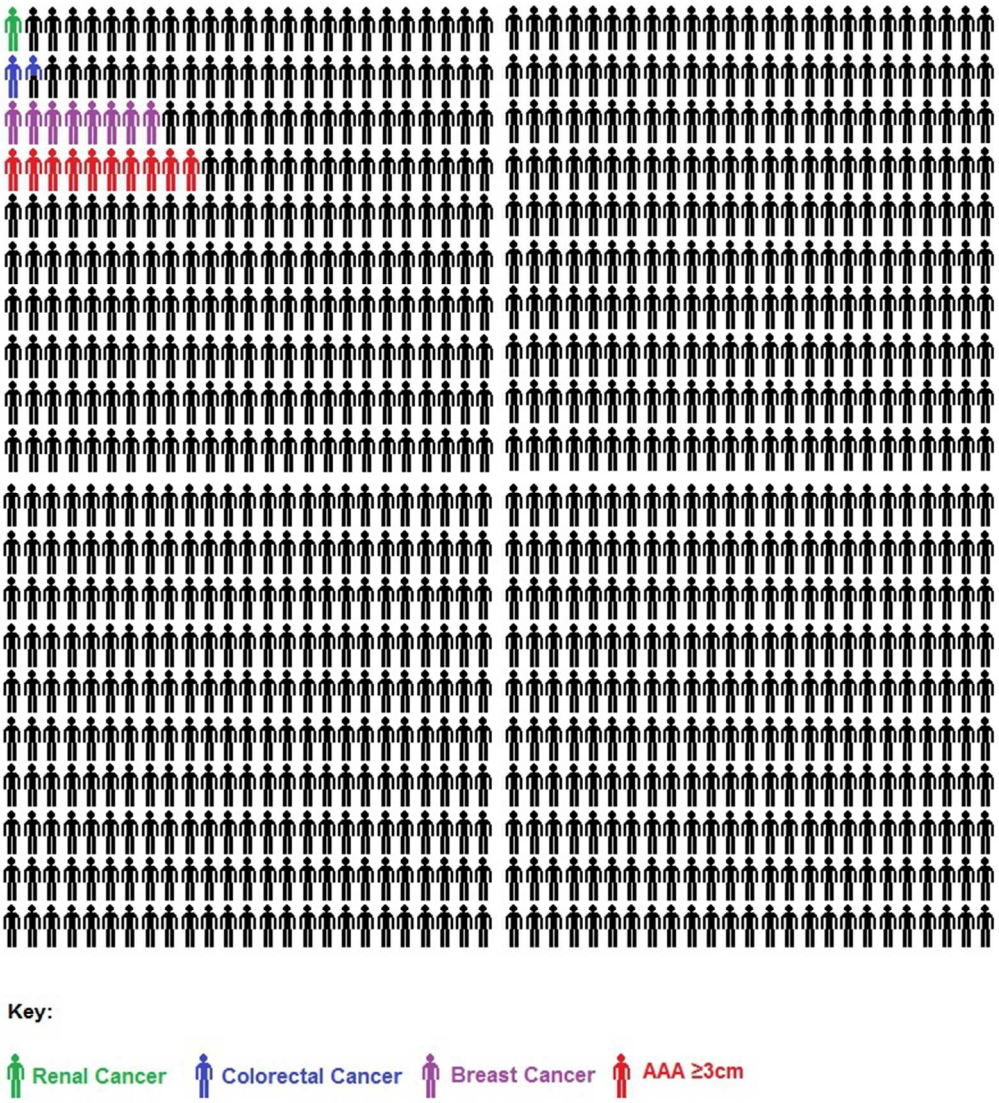

Figure 4: Infographic delineating comparative detecting ability of established UK screening programs versus screening for renal cell carcinoma. Our meta-analysis suggests screening 1 000 individuals would detect at least 1 renal cell carcinoma (green). Screening 1 000 individuals detects 1.6 colorectal cancers (blue), 8 breast cancers (pink) and 10 abdominal aortic aneurysms ≥ 3cm (red).

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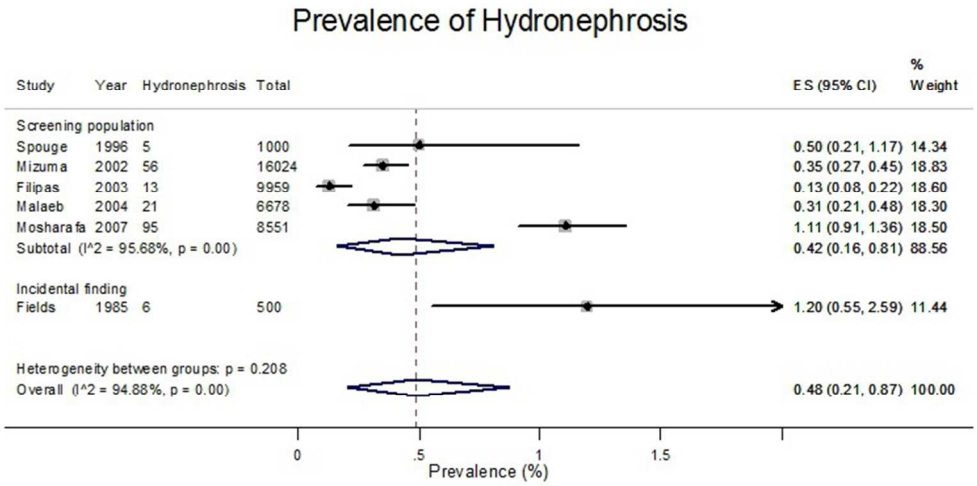

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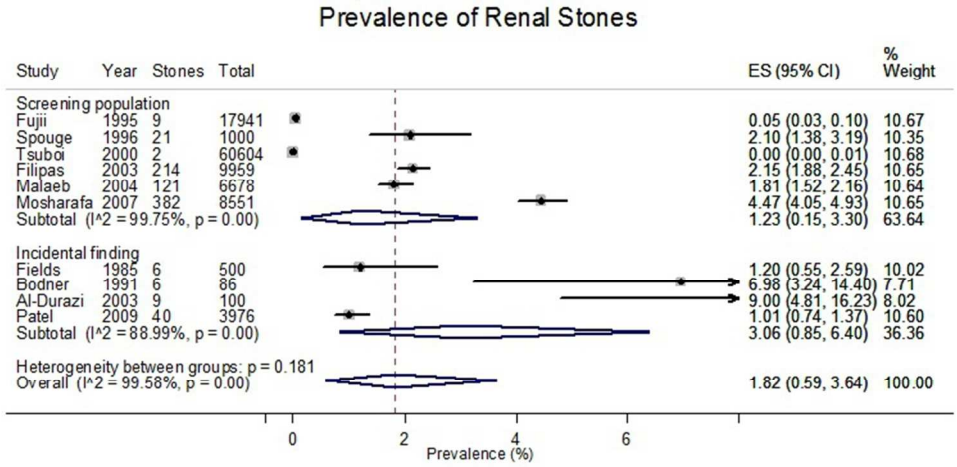

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Supplementary Tables

Supplementary Table S1

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table S2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table S4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 2-3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figures 2-3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-11, Table S7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Supplementary Table S2

Search	Database and dates	Search terms
Search #1	Medline (1976-March 2016)	Kidney neoplasms (Medical Subject Heading) OR renal cell carcinoma OR RCC OR renal mass$ OR renal cancer OR renal neoplas$ OR renal tumo?r OR renal carcinoma OR kidney cancer OR kidney neoplas$ OR kidney tumo?r OR kidney carcinoma OR hypernephroma OR Grawitz tumor OR renal adenocarcinoma OR oncocytoma AND Mass screening (Medical Subject Heading) or screen$ AND Ultrasonography (Medical Subject Heading) OR ultraso$
Search #2	Medline (1976-March 2016)	Kidney neoplasms (Medical Subject Heading) OR renal cell carcinoma OR RCC OR renal mass$ OR renal cancer OR renal neoplas$ OR renal tumo?r OR renal carcinoma OR kidney cancer OR kidney neoplas$ OR kidney tumo?r OR kidney carcinoma OR hypernephroma OR Grawitz tumor OR renal adenocarcinoma OR oncocytoma AND Mass screening (Medical Subject Heading) or screening
Search #3	Medline (1976-March 2016)	Kidney neoplasms (Medical Subject Heading) OR renal cell carcinoma OR RCC OR renal mass$ OR renal cancer OR renal neoplas$ OR renal tumo?r OR renal carcinoma OR kidney cancer OR kidney neoplas$ OR kidney tumo?r OR kidney carcinoma OR hypernephroma OR Grawitz tumor OR renal adenocarcinoma OR oncocytoma AND Incidental finding (Medical Subject Heading) OR incidental$ OR prevalence ((Medical Subject Heading) OR prevalence
Search #4	Embase (1976-March 2016)	Kidney neoplasms (Medical Subject Heading) OR renal cell carcinoma OR RCC OR renal mass$ OR renal cancer OR renal neoplas$ OR renal tumo?r OR renal carcinoma OR kidney cancer OR kidney neoplas$ OR kidney tumo?r OR kidney carcinoma OR hypernephroma OR Grawitz tumor OR renal adenocarcinoma OR oncocytoma AND Screening (Medical Subject Heading) OR mass screening (Medical Subject Heading) OR cancer screening (Medical Subject Heading) OR screen$ AND Ultrasound (Medical Subject Heading) OR ultraso$

Supplementary Table S3

Inclusion Criteria	Exclusion Criteria
1) Study reporting prevalence of renal masses and/or renal cell carcinoma in asymptomatic individuals undergoing ultrasonography. 2) Study reporting prevalence of renal masses and/or renal cell carcinoma in patients undergoing ultrasound for abdominal symptoms not related to renal cell carcinoma. 3) Adult population (age >15 years) 4) Publication year after 1976 5) English language 6) Where several studies reported data on the same population, only the larger and more recent of these was included in the analysis.	1) Study in which ultrasound was performed in individuals that did not represent a general unselected adult population a. End stage renal failure b. Dialysis c. Renal transplant d. Von Hippel Lindau disease or familial syndromes predisposing to renal cancer 2) Study in which ultrasound was performed in patients with symptoms suggestive of renal cancer a. Flank pain b. Abdominal mass c. Microscopic or macroscopic haematuria 3) Study in which ultrasound was performed in patients with suspected renal colic (as symptoms may have been secondary to RCC rather than renal stone) 4) Whilst calculating the pooled prevalence of hydronephrosis, we exclude data from studies on patients with lower urinary tract symptoms [1] as these may over-estimate the prevalence of this condition in a general population.

Supplementary Table S4

	Random sample?	Screening vs non-screening population?	Adequacy of sample size?	Histology-proven RCC?	Unbiased ultrasound assessment?	Response rate described and adequate?	Results with confidence intervals?	Subjects similar to population of interest?	Total Quality Score (n/N)
Screening Population									
Fujii (1995)	0	1	1	1	1	0	0	1	5/8
Spouge (1996)	0	1	1	1	1	0	0	0	4/8
Mihara (1999)	0	1	1	1	1	0	0	0	4/8
Tsuboi (2000)	0	1	1	1	1	0	0	1	5/8
Mizuma (2002)	0	1	1	1	1	0	0	0	4/8
Filipas (2003)	0	1	1	1	1	1	0	1	6/8
Malaeb (2004)	0	1	1	1	1	0	0	1	5/8
Mosharafa (2007)	0	1	1	0	1	0	0	0	3/8
Mixed									
Tosaka (1990)	0	0	1	1	1	0	0	0	3/8
Haliloglu (2010)	0	0	1	1	1	0	0	1	4/8
Incidental finding									
Fields (1985)	0	0	0	0	1		0	0	1/7
Bodner (1991)	0	0	0	0	1		0	0	1/7
Al-Durazi (2003)	0	0	0	0	1		0	1	2/7
Belani (2004)	0	0	0	0	1		0	0	1/7
Heikkinen (2005)	0	0	0	1	1		0	0	2/7
Patel (2009)	0	0	0	1	1		0	1	3/7

Supplementary Table S5

Data on tumour size	Data on tumour size	Data on tumour stage
Total sample size: 66 Source: [2-5]	Total: 185 Source: [6, 7]	Total sample size: 205 TNM 1992 classification Source: [2, 3, 6]
<4cm: 30/66 =45% 4-7cm: 27/66 =41% 7-10= 7/66 =11% >10: 2/66= 3%	<5cm = 148/185=80% >5: 37/185= 20%	T1= 65/205 = 32% T2 =108/205 = 52.5% T3N0=27/205 = 13% T4N0=1/205 = 0.5% T3N+=2/205=1% Metastases: 2/205 = 1%

Supplementary Table S6

Study (year)	Sample size N	Prevalence of benign pathology n (%)	Prevalence of malignant pathology n (%)
Fuji (1995)	17941	1 (0.0056%) Renal leiomyoma 1 (0.0056%) Renal hemangioma 41 (0.23%) AML 9 (0.05%) Stones 24 (0.13%) Normal variant/Cyst 7 (0.039%) Pseudotumour Total: 83 (0.46%) (note: 41 suspected AML but only 24 real confirmed)	
Spouge (1996)	1,000	8 (0.8%) AML 21 (2.1%) Stones 5 (0.5%) Hydronephrosis 73 (7.3%) Simple cyst (But on follow up imaging none were confirmed hydronephrosis) (12 (1.2%) Complex cyst)	1 (0.1%) TCC bladder 1 (0.1%) Suspicious adrenal mass
Mihara (1999)	219,640	84 (0.038%) AML/other benign tumours 59 (0.027%) Renal cysts 5 (0.0023%) Borderline lesions 4 (0.0018%) Deformity of the kidney	Suspicious Pancreatic mass:1 Atypical hepatic hemangioma: 4 1 (0.00046%) Renal pelvic cancer 2 (0.00091%) Sarcoma 1 (0.00046%) Renal carcinoid 1 (0.00046%) Malignant lymphoma of the kidney 228 HCC liver 90 Gallbladder cancers 68 Pancreatic cancers
Tsuboi (2000)	60,604	24 (0.040%) AML 2 (0.0033%) Stones 2 (0.0033%) Complex cysts	
Mizuma (2002)	16,024	56 (0.35%) Hydronephrosis 31 (0.19%) Renal abnormality requiring further investigation	1 Bladder cancer

Filipas (2003)	9,959	1 (0.010%) Oncocytoma 9 (0.090%) AML 13 (0.13%) Hydronephrosis 214 (2.1%) Stones 40 (0.40%) Renal anomaly (small kidney, dysplasia, aplasia) 1264 (12.69%) Cyst/scar/duplex system	
Malaeb (2004)	6,678	627 (9.4%) Simple cysts 21 (0.31%) Hydronephrosis 121 (1.8%) Stones 24 (0.36%) Other renal abnormality (horseshoe kidney, atrophy, duplication, renal calcifications)	2 (0.030%) Suspicious adrenal mass
Mosharafa (2007)	8,551	360 (4.2%) Simple cyst 19 (0.22%) Renal Atrophy 382 (4.5%) Stones 95 (1.1%) Hydronephrosis 83 (0.97%) Increased parenchymal echogenicity	
Tosaka (1990)	41,364 (20,897 screening and 20,467 non screening)	82 (0.20%) Cyst 8 (0.019%) AML 2 (0.0048%) Other benign neoplasm 8 (0.019%) Other benign lesion 12 (0.029%) Sinus lipomatosis	
Haliloglu (2010)	18,203	35 (0.19%) AML 3 (0.016%) Indeterminate benign cyst	
Matthews (1982)	100	15 (15%) Cyst 1 (1%) Small kidney	
Fields (1985)	500	(*Hydronephrosis data excluded as LUTS = Mild hydronephrosis in 5, Severe in 5) 33 (6.6%) Cyst 6 (1.2%) Hydronephrosis 6 (1.2) Stones 5 (1%) Chronic renal disease 1 (0.2%) Extrarenal pelvis 1 (0.2%) Malrotated kidney	

Bodner (1990)	86 Spinal cord injury patients*	6 (7.0%) Cyst 6 (7.0%) Stones 8 (9.3%) Chronic pyelonephritis *Hydronephrosis likely overestimated, as are 3 Bladder stones and 3 Bladder diverticiculae	
Al-durazi (2003)	100	9 (9%) Stones 9 (9%) Cyst 2 (2%) small kidneys *Hydronephrosis overestimated in this group, as are bladder stones 5	2 (2%) Bladder cancer
Belani (2004)	600	4 (0.67%) AML	
Heikinnen (2005)	400	1 (0.25%) AML, 32 (8%) Cysts 12 (3%) Abnormal kidney size/shape/echogenicity 18 (4.5%) Abnormal renal pelvis/sinus. 34 (8.5%) Focal renal lesions (not specified)	
Patel (2009)	3,976	14 (0.35%) Cyst 40 (1.0%) Stones *Hydronephrosis will be overestimated, as will be bladder stones	1 (0.025%) Metastatic lymphomatous adrenal lesion

Abbreviations: AML=angiomyolipoma; LUTS= lower urinary tract symptoms; TCC= transitional cell carcinoma.

Supplementary Table S7

Variable	Coefficient	Standard error	P value
Study type (screening population, incidental finding and mixed)	0.000087	0.00054	0.876
Publication year	-0.00065	0.000091	<0.0001
Study quality score	0.00049	0.00059	0.432
Geographical region	0.0012	0.00027	0.002
Constant	-0.00029	0.00089	0.753

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