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The IDENTIFY study: the investigation and detection of urological neoplasia in patients referred with suspected urinary tract cancer – a multicentre observational study

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Objective

To evaluate the contemporary prevalence of urinary tract cancer (bladder cancer, upper tract urothelial cancer [UTUC] and renal cancer) in patients referred to secondary care with haematuria, adjusted for established patient risk markers and geographical variation.

Patients and Methods

This was an international multicentre prospective observational study. We included patients aged ≥16 years, referred to secondary care with suspected urinary tract cancer. Patients with a known or previous urological malignancy were excluded. We estimated the prevalence of bladder cancer, UTUC, renal cancer and prostate cancer; stratified by age, type of haematuria, sex, and smoking. We used a multivariable mixed-effects logistic regression to adjust cancer prevalence for age, type of haematuria, sex, smoking, hospitals, and countries.

Results

Of the 11 059 patients assessed for eligibility, 10 896 were included from 110 hospitals across 26 countries. The overall adjusted cancer prevalence (n = 2257) was 28.2% (95% confidence interval [CI] 22.3–34.1), bladder cancer (n = 1951) 24.7% (95% CI 19.1–30.2), UTUC (n = 128) 1.14% (95% CI 0.77–1.52), renal cancer (n = 107) 1.05% (95% CI 0.80–1.29), and prostate cancer (n = 124) 1.75% (95% CI 1.32–2.18). The odds ratios for patient risk markers in the model for all cancers were: age 1.04 (95% CI 1.03–1.05; $P < 0.001$), visible haematuria 3.47 (95% CI 2.90–4.15; $P < 0.001$), male sex 1.30 (95% CI 1.14–1.50; $P < 0.001$), and smoking 2.70 (95% CI 2.30–3.18; $P < 0.001$).

Conclusions

A better understanding of cancer prevalence across an international population is required to inform clinical guidelines. We are the first to report urinary tract cancer prevalence across an international population in patients referred to secondary care, adjusted for patient risk markers and geographical variation. Bladder cancer was the most prevalent disease. Visible haematuria was the strongest predictor for urinary tract cancer.

Keywords

haematuria, bladder cancer, upper tract urothelial cancer, renal cancer, cancer prevalence, hematuria, urinary tract cancer, prostate cancer

INTRODUCTION

Urinary tract cancers are associated with a significant morbidity and mortality, and their prevalence varies globally [1,2]. The majority of urinary tract cancers consist of bladder cancers, with the minority consisting of upper tract urothelial carcinoma (UTUC) and renal cancers [3].

Haematuria is the most common presentation of suspected urinary tract cancers and is the leading cause of referral to secondary care amongst the urological cancer pathways [4,5]. This poses a huge global health burden [6]. Haematuria can be classified into visible (macroscopic or gross) haematuria (VH) and non-visible (microscopic or dipstick) haematuria (NVH). Other causes of haematuria should be considered including benign pathology and uncommonly, prostate cancer in men. There is a higher rate of urinary tract cancer in patients with VH compared to NVH, and this is a known predictor of urinary tract cancer [7–9]. Other known risk markers are important to consider including age, smoking and male sex, which have been associated with urinary tract cancer, with variation in the reported strength of association [10–12].

Cancer prevalence data can inform clinical guidelines on referral of patients for investigation of suspected urinary tract cancer, as shown by the systematic review used for informing AUA guidelines [13]. The majority of the evidence used is from secondary care data, including several prospective and retrospective cohort studies [3,8,9,14]. However, these have been smaller and geographically limited studies. Furthermore, they only report crude estimates of cancer prevalence and have not adjusted for well-known risk markers or geographical variation in multicentre studies.

The IDENTIFY study is the largest prospective study of patients referred with suspected urinary tract cancer, which evaluated a globally diverse population. Our primary objective was to assess the contemporary prevalence of bladder cancer, UTUC, renal cancer and prostate cancer in patients referred to secondary care with suspected urinary tract cancer. Our secondary objectives were to assess the prevalence of these cancers in patients referred with VH and NVH across different age groups, sex and smoking status, and report the adjusted prevalence to inform evidence-based updates of referral guidelines.

PATIENTS AND METHODS

Study Design and Setting

The IDENTIFY study was an international prospective cohort study conducted by the British Urology Researchers in Surgical Training (BURST) collaborative group [15]. The protocol for the study has been published [16]. The study evaluated patients referred to secondary care for suspected urinary tract cancer, predominantly with haematuria. Participating collaborators completed a registration survey describing their typical protocol for the investigation of haematuria at their hospital (Appendix S1). Patient data were obtained from hospital records of consecutive patients attending a secondary care 'haematuria clinic' for a diagnostic cystoscopy between December 2017 and December 2018. Patients were followed-up until their haematuria investigations were concluded and a diagnosis confirmed or ruled out, as per the judgement of the clinical care team. The study was closed in February 2019. We report this study

according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Appendix S1) [17].

Participants

We included patients aged ≥16 years, with haematuria or with no haematuria (NH), referred to a urologist for the investigation of suspected urinary tract cancer (defined as bladder cancer, UTUC or renal cancer). Patients were excluded if they had a previous or known diagnosis of primary urological cancer or were undergoing investigations for recurrence of a primary urological cancer.

Outcomes

The primary outcome was the prevalence of bladder cancer, UTUC, renal cancer and prostate cancer in patients referred to secondary care with suspected urinary tract cancer. We define cancer prevalence as detected cases within the defined population (patients referred to secondary care), which is consistent with terminology used in previous published literature [8]. Prostate cancer typically follows a different referral pathway and is not included in our definition of suspected urinary tract cancer; however, we report its prevalence of cancer based on its identification in the pilot study [16]. Our secondary outcomes were the prevalence of these cancers in patients stratified by and adjusted for type of haematuria, age, sex and smoking status, as these are well-established markers of cancer.

Diagnostic Criteria: Cancer Classification

Patients were classified as being cancer positive or cancer negative for the calculation of prevalence. We determined the case definitions for bladder cancer, renal cancer, UTUC and prostate cancer before analysis of prevalence (Table S1). Pathological definitions were based on the WHO cancer classification system [18,19]. Patients with histological or clinical evidence for cancer after multidisciplinary team (MDT) review were classified as cancer positive, whilst those with negative investigations for cancer, or without sufficient clinical evidence for a finding to be determined as cancer were classified as cancer negative. Definitions were in accordance with current clinical practice in the management of patients with urinary tract cancer.

Data Collection

Data collected included the reason for referral, baseline demographic information, clinical history, urine analysis, cytology, imaging findings, cystoscopy findings, histopathology from biopsies or surgery, and MDT decisions [16]. Type of haematuria was determined by the primary care referral letter and/or the history obtained from the patient at the time of assessment in secondary care. NVH was defined by a trace or more on urine dipstick, or >3 red blood cells/high-power field [20]. Smoking status was categorised into current smoker, ex-smoker, and never smoked. All site data were verified for completeness by an independent quality control team.

Sample Size

Sample size was determined *a priori*. Based on the overall prevalence of urological malignancy of 12% from our pilot study [16], a minimum sample size of 5000 patients was required to give a 95% CI with a precision of ± 0.01% for the estimate of cancer prevalence.

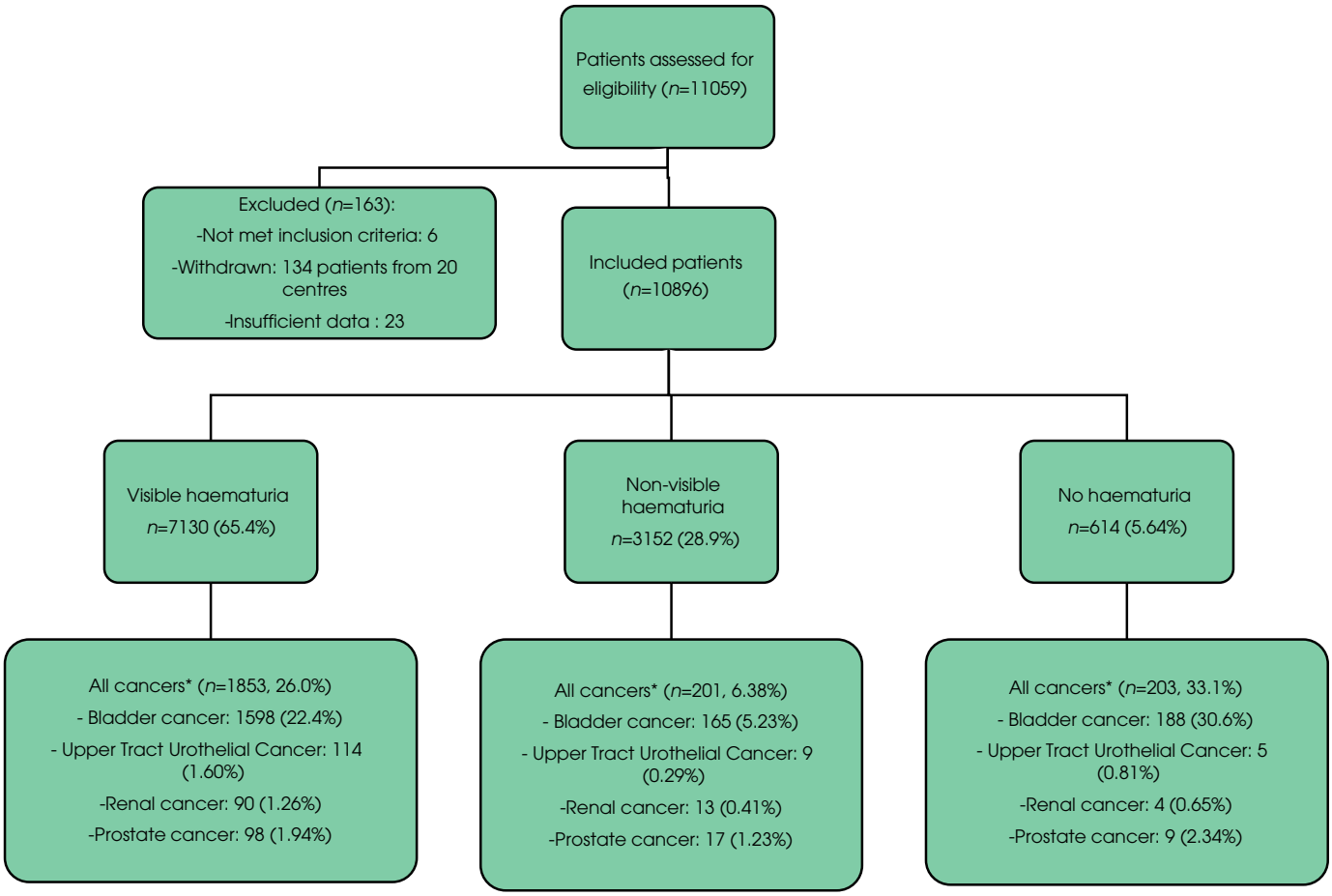
Statistical Analysis

Unadjusted estimates of urinary tract cancer prevalence were calculated as proportions of the total number of patients with the target disease in a cohort (total number of patients at risk). The CIs were calculated using the Wilson method [21,22]. Patients with NH were included in this analysis for completeness. These patients typically have an incidental finding of cancer on imaging and are referred through the haematuria pathway for confirmation. However, they were not included in the secondary outcomes as we deemed them a distinct patient group. We also estimated prevalence separately for patients with VH and NVH. NVH was not subdivided into asymptomatic NVH and symptomatic NVH, as there is no agreement on which symptoms are included in symptomatic NVH [23]. Within each type of haematuria, we stratified prevalence by cancer type, sex, age group, and smoking status. The first age group was defined as aged <35 years to reflect the lowest age threshold used in international guidelines [3,24]. Age bins of 5 years were chosen, as this was the common denominator to match different international guideline age thresholds. Analyses of prostate cancer only included male patients.

We adjusted the cancer prevalence for four predetermined risk markers (type of haematuria, age, sex, and smoking) using a mixed-effects logistic regression model that included country and centre as random effects to adjust for country and centre variation in prevalence. Age was analysed as a continuous variable. Risk markers were chosen on basis of prior evidence and biological plausibility for their association with urinary tract cancer detection. Adjusted estimates of prevalence were obtained from these models.

We did not impute missing data and all analyses were performed using Stata version 16.1 (StataCorp, College Station, TX, USA). A $P < 0.05$ was deemed statistically significant.

Fig. 1 Cohort flow diagram. *Some patients were found to have more than one type of cancer, therefore the total number of patients with cancer (i.e. 'All cancers') do not equal the sum of the different types of cancer within that box.



*Some patients were found to have more than one type of cancer, therefore the total number of patients with cancer (i.e. 'All cancers') do not equal the sum of the different types of cancer within that box.

Data Handling and Ethics

Anonymised patient data were securely collected from routinely documented information during the investigation of haematuria and patient records were accessed only by the direct clinical care team. In the UK, the coordinating centre, The Royal Devon and Exeter NHS Foundation Trust Research and Development board, deemed the IDENTIFY study to be exempt from ethical approval and it was given approval as a service evaluation consistent with UK Health Research Authority guidelines. Participating institutions registered the study locally with their Research and Development, and approval for study participation was granted at each centre.

This study was registered with clinicaltrials.gov NCT03548688.

RESULTS

Of 11 059 patients assessed for eligibility, we included 10 896 patients from 110 hospitals across 26 countries (Table S2 and Table S3 details the number of patients and cancers in each country/site). About two-thirds (65.4%) of patients were referred with VH and 28.9% with NVH (Fig. 1). The remaining (5.64%) patients had NH and reasons for their referral are given in Table S4.

Patient demographics and clinical characteristics are shown in Table 1. The cancer classifications are detailed in Table S5. Of the 10 896 patients, 2257 had cancer (overall prevalence of 20.7%, 95% CI 20.0–21.5), the majority of which was bladder cancer (n = 1951), with a prevalence of 17.9% (95% CI 17.2–18.6). The other types of cancer were less common; prevalence of UTUC (n = 128) was 1.17% (95% CI 0.99–

Table 1 Patient demographics and clinical characteristics.

	Total, *n* (%)	No cancer, *n* (%)	All cancers, *n* (%)	Bladder cancer, *n* (%)	UTUC, *n* (%)	Renal cancer, *n* (%)	Prostate cancer, *n* (%)
Total	10896	8639 (79.3)	2257 (20.7)	1951 (17.9)	128 (1.17)	107 (0.98)	124/6807 (1.82)
Type of haematuria							
NVH	3152 (28.9)	2951 (34.2)	201 (8.91)	165 (8.46)	9 (7.03)	13 (12.1)	17 (13.7)
VH	7130 (65.4)	5277 (61.1)	1853 (82.1)	1598 (81.9)	114 (89.1)	90 (84.1)	98 (79.0)
NH	614 (5.64)	411 (4.76)	203 (8.99)	188 (9.64)	5 (3.91)	4 (3.74)	9 (7.26)
Age, years							
Mean (SD)	64.4 (14.4)	62.8 (14.8)	70.4 (12.0)	70.5 (11.8)	71.6 (11.8)	64.6 (13.0)	72.7 (11.0)
<35	413 (3.79)	394 (4.56)	19 (0.84)	15 (0.77)	2 (1.56)	1 (0.93)	1 (0.81)
35–39	261 (2.40)	242 (2.80)	19 (0.84)	17 (0.87)	1 (0.78)	2 (1.87)	0 (0)
40–44	379 (3.48)	353 (4.09)	26 (1.15)	23 (1.18)	1 (0.78)	2 (1.87)	1 (0.81)
45–49	621 (5.70)	566 (6.55)	55 (2.44)	45 (2.31)	1 (0.78)	6 (5.61)	3 (2.42)
50–54	922 (8.46)	819 (9.48)	103 (4.56)	83 (4.25)	4 (3.12)	15 (14.0)	1 (0.81)
55–59	1137 (10.4)	988 (11.4)	149 (6.60)	122 (6.25)	10 (7.81)	14 (13.1)	5 (4.03)
60–64	1322 (12.1)	1067 (12.4)	255 (11.3)	226 (11.6)	11 (8.59)	14 (13.1)	11 (8.87)
65–69	1432 (13.1)	1092 (12.6)	340 (15.1)	296 (15.2)	18 (14.1)	12 (11.2)	24 (19.4)
70–74	1514 (13.9)	1112 (12.9)	402 (17.8)	344 (17.6)	24 (18.8)	17 (15.9)	22 (17.7)
≥75	2894 (26.6)	2005 (23.2)	889 (39.4)	780 (40.0)	56 (43.8)	24 (22.4)	56 (45.2)
Sex							
Female	4080 (37.4)	3558 (41.2)	522 (23.1)	463 (23.7)	42 (32.8)	26 (24.3)	NA
Male	6807 (62.5)	5075 (58.8)	1732 (76.7)	1485 (76.1)	86 (67.2)	81 (75.7)	124 (100)
Other	9 (0.08)	6 (0.07)	3 (0.13)	3 (0.15)	0 (0)	0 (0)	0 (0)
Smoking							
Never smoked	4877 (44.8)	4219 (48.8)	658 (29.2)	526 (27.0)	41 (32.0)	45 (42.1)	61 (49.2)
Ex-smoker	3231 (29.7)	2374 (27.5)	857 (38.0)	765 (39.2)	40 (31.3)	39 (36.5)	36 (29.0)
Current smoker	1991 (18.3)	1421 (16.5)	570 (25.3)	516 (26.5)	37 (28.9)	17 (15.9)	12 (9.68)
Unknown	797 (7.31)	625 (7.23)	172 (7.62)	144 (7.38)	10 (7.81)	6 (5.61)	15 (12.1)
Smoking pack years (*n* = 6019)							
0–10	996 (16.5)	792 (17.9)	204 (12.8)	174 (12.2)	15 (17.2)	9 (14.5)	8 (12.7)
11–20	1060 (17.6)	727 (16.5)	333 (20.8)	308 (21.6)	18 (20.7)	8 (12.9)	9 (14.3)
>20	1921 (31.9)	1242 (28.1)	679 (42.5)	616 (43.2)	34 (39.1)	29 (46.8)	19 (30.2)
Unknown	1049 (17.4)	865 (19.6)	184 (11.5)	160 (11.2)	10 (11.5)	9 (14.5)	9 (14.3)
Missing	993 (16.5)	794 (18.0)	199 (12.4)	167 (11.7)	10 (11.5)	7 (11.3)	18 (28.6)
UTI history							
None	8334 (76.5)	6340 (73.4)	1994 (88.4)	1724 (88.4)	114 (89.1)	96 (89.7)	106 (85.2)
Single	1291 (11.9)	1147 (13.3)	144 (6.38)	120 (6.15)	9 (7.03)	6 (5.61)	12 (9.68)
Recurrent	1127 (10.3)	1028 (11.9)	99 (4.39)	87 (4.46)	5 (3.91)	5 (4.67)	6 (4.84)
Missing	144 (1.32)	124 (1.44)	20 (0.89)	20 (1.03)	0 (0)	0 (0)	0 (0)
UTI at time of haematuria *n*/*N* with UTI (%)	1580/2418 (65.3)	1437/2175 (66.1)	143/243 (58.8)	118/207 (57.0)	10/14 (71.4)	8/11 (72.7)	10/18 (55.6)
Body mass index (BMI), kg/m^2							
Mean (SD)	27.4 (5.67)	27.7 (5.94)	26.8 (4.84)	26.7 (4.80)	26.3 (4.77)	27.9 (5.89)	26.9 (4.73)
Not obese (BMI <30)	3868 (35.5)	2685 (31.1)	1183 (52.4)	1051 (53.9)	71 (55.5)	41 (38.3)	53 (42.7)
Obese (BMI ≥30)	1346 (12.4)	1045 (12.1)	301 (13.3)	261 (13.4)	14 (11.0)	18 (16.8)	13 (10.5)
Missing	5682 (52.1)	4909 (56.8)	773 (34.3)	639 (32.8)	43 (33.6)	48 (44.9)	58 (46.8)
Ethnicity							
White	8469 (77.7)	6574 (76.1)	1895 (84.0)	1648 (84.5)	112 (87.5)	88 (82.2)	96 (77.4)
Asian	1239 (11.4)	1033 (12.0)	206 (9.13)	185 (9.48)	6 (4.69)	8 (7.48)	9 (7.26)
Black	305 (2.80)	282 (3.26)	23 (1.02)	14 (0.72)	3 (2.34)	3 (2.80)	3 (2.42)
Other	533 (4.89)	446 (5.16)	87 (3.85)	65 (3.33)	4 (3.12)	5 (4.67)	14 (11.3)
Missing	350 (3.21)	304 (3.52)	46 (2.04)	39 (2.00)	3 (2.34)	3 (2.80)	2 (1.61)
Occupational risk*							
No	9061 (83.2)	7211 (83.5)	1850 (82.0)	1592 (81.6)	105 (82.0)	94 (87.9)	103 (83.1)
Yes	420 (3.85)	290 (3.36)	130 (5.76)	121 (6.20)	5 (3.91)	2 (1.87)	6 (4.84)
Unknown	1060 (9.73)	828 (9.58)	232 (10.3)	201 (10.3)	15 (11.7)	9 (8.41)	11 (8.87)
Missing	355 (3.26)	310 (3.59)	45 (1.99)	37 (1.90)	3 (2.34)	2 (1.87)	4 (3.23)
Medication risk†							
No	9757 (89.6)	7734 (89.5)	2023 (89.6)	1752 (89.9)	110 (85.9)	97 (90.7)	113 (91.1)
Yes	84 (0.77)	62 (0.72)	22 (0.97)	18 (0.92)	2 (1.56)	1 (0.93)	1 (0.81)
Unknown	672 (6.17)	506 (5.86)	166 (7.35)	145 (7.43)	11 (8.59)	7 (6.54)	6 (4.84)
Missing	383 (3.52)	337 (3.90)	46 (2.04)	36 (1.85)	5 (3.91)	2 (1.87)	4 (3.23)
Dysuria							
No	8391 (77.0)	6528 (75.6)	1863 (82.5)	1601 (82.1)	116 (90.6)	88 (82.2)	100 (80.65)
Yes	2270 (20.8)	1907 (22.1)	363 (16.1)	320 (16.4)	11 (8.56)	19 (17.8)	24 (19.4)
Missing	235 (2.16)	204 (2.36)	31 (1.37)	30 (1.54)	1 (0.78)	0 (0)	0 (0)

Table 1 (continued)

	Total, *n* (%)	No cancer, *n* (%)	All cancers, *n* (%)	Bladder cancer, *n* (%)	UTUC, *n* (%)	Renal cancer, *n* (%)	Prostate cancer, *n* (%)
Raised WCC							
No	5920 (54.3)	4470 (51.7)	1450 (64.2)	1265 (64.8)	89 (69.5)	63 (58.9)	69 (55.7)
Yes	621 (5.70)	438 (5.07)	183 (8.11)	157 (8.05)	13 (10.2)	13 (12.1)	7 (5.65)
Missing	4355 (40.0)	3731 (43.2)	624 (27.7)	529 (27.1)	26 (20.3)	31 (29.0)	48 (38.7)
Previous haematuria evaluation							
No	9709 (89.1)	7607 (88.1)	2102 (93.1)	1823 (93.4)	119 (93.0)	100 (93.5)	109 (87.9)
Yes	1053 (9.66)	917 (10.6)	136 (6.03)	109 (5.59)	9 (7.03)	7 (6.54)	15 (12.1)
Missing	134 (1.23)	115 (1.33)	19 (0.84)	19 (0.97)	0 (0)	0 (0)	0 (0)

*NA, not applicable; WCC, white cell count. Percentages are column percentages except in the first row ('Total'), which are row percentages. *Defined as exposure to dyes, rubber, textiles, pesticides. †e.g. cyclophosphamide, pioglitazone.*

1.39), renal cancer (n = 107) was 0.98% (95% CI 0.80–1.29), and prostate cancer (n = 124) was 1.82% (95% CI 1.51–2.17).

Proportions of urinary tract cancers (bladder cancer, UTUC, and renal cancer) by type of haematuria for different age groups, sex, and smoking status are shown in Table 2a and 2b. Patients with VH had an overall cancer prevalence of 26.0% compared to 6.38% in patients with NVH. Irrespective of the type of haematuria, the proportion of cancer appeared to increase with age, those with a smoking history, and in males. In patients with NVH there were no cancers in those aged <35 years, nor renal cancers in those aged <40 years or UTUCs those aged <60 years. In patients with VH, the overall cancer prevalence was 17.8% in never smokers vs 35.7% in current smokers, and 19.9% in females vs 28.5% in males.

In patients with any haematuria (VH or NVH) the adjusted prevalence of bladder cancer was 24.7% (95% CI 19.1–30.2) in comparison to unadjusted prevalence of 17.1% (95% CI 16.4–17.9) (Table 3). Adjusted prevalence of bladder cancer was also higher than the unadjusted prevalence in both the VH and NVH groups. Adjusted and unadjusted prevalence rates were similar for UTUC, renal cancer, and prostate cancer.

The multivariable mixed-effects logistic regression used for adjustment showed that VH, older age, male sex, and smoking were significant risk markers for 'all cancers' (Table 4). Considering each cancer type separately, VH was significantly associated with bladder cancer (odds ratio [OR] 3.50, 95% CI 2.88–4.26; $P < 0.001$), UTUC (OR 4.23, 95% CI 2.09–8.55; $P < 0.001$), and renal cancer (OR 2.56, 95% CI 1.40–4.67; $P < 0.001$). Increasing age (OR 1.04, 95% CI 1.03–1.06; $P < 0.001$) also increased the odds of bladder cancer, UTUC, and prostate cancer. Compared to patients who had never smoked, ex-smokers and current smokers had significantly increased odds of bladder cancer and UTUC, with current smokers having more than a three-fold increase in the odds of bladder cancer (OR 3.18, 95% CI 2.67–3.78). Male sex was associated with bladder cancer (OR 1.15, 95% CI 1.00–1.34; $P = 0.058$) and renal cancer (OR 1.54, 95% CI 0.95–2.49; $P = 0.08$), but these were not statistically significant.

DISCUSSION

The IDENTIFY study is the largest international prospective observational study on the investigation of suspected urinary tract cancer in secondary care. Bladder cancer was the most common cancer, with an adjusted prevalence of 24.7% in patients with haematuria. The rarer upper tract cancers, UTUC and renal cancer, accounted for ~1% each. Urinary tract cancers were more prevalent in patients with VH, men, older patients, and those with a smoking history. These factors were significantly associated with urinary tract cancer on multivariable analysis. There were no cancers in the NVH group in patients aged <35 years for bladder cancer or those aged <60 years for UTUC. These data can become the new reference standard to inform international guidelines for the investigation of urinary tract cancer.

The main strength of the present study is its design and robust methods in estimating an adjusted prevalence of disease. The study's large sample size allowed for estimates with a high degree of precision, especially in rarer cancers. The international nature of the present study and the breadth of countries improves on previous single-centre studies in this field [3,8,9]. To our knowledge, we are the first to adjust cancer prevalence for well-known patient risk markers and geographical variation. Our methods show transparency of cancer classification, and we have minimised selection bias by including an international population that would typically be encountered in clinical practice.

A multicentre study in secondary care reported a much lower bladder cancer crude prevalence of 8.0% in patients being investigated with haematuria [3]. However, the primary objective of that previous study was not to determine the prevalence of urinary tract cancer, nor was the study designed to. Patients were recruited as part of a urinary biomarker

Table 2 Proportion of urinary tract cancers stratified by type of haematuria.

(a)	Visible haematuria, n (%)				
	Total patients	**All cancers**	**Bladder cancer**	**UTUC**	**Renal cancer**
Total	7130	1853 (26.0)	1598 (22.4)	114 (1.60)	90 (1.26)
Age					
<35	275 (3.86)	17 (6.18)	13 (4.73)	2 (0.73)	1 (0.36)
35–39	164 (2.30)	13 (7.93)	12 (7.32)	0 (0)	2 (1.22)
40–44	228 (3.20)	22 (9.65)	19 (8.33)	1 (0.44)	2 (0.88)
45–49	371 (5.20)	44 (11.9)	37 (9.97)	1 (0.27)	5 (1.35)
50–54	524 (7.32)	84 (16.0)	67 (12.8)	4 (0.76)	13 (2.48)
55–59	671 (9.41)	112 (17.0)	91 (13.6)	10 (1.49)	9 (1.34)
60–64	827 (11.6)	210 (25.4)	186 (22.5)	9 (1.09)	11 (1.36)
65–69	930 (13.1)	273 (29.4)	239 (25.7)	15 (1.61)	11 (1.18)
70–74	1012 (14.2)	333 (32.9)	283 (28.0)	22 (2.17)	16 (1.58)
≥75	2127 (29.8)	745 (35.0)	651 (30.6)	50 (2.35)	20 (0.94)
Sex					
Female	2083 (29.2)	415 (19.9)	367 (17.6)	36 (1.73)	20 (0.96)
Male	5043 (70.7)	1437 (28.5)	1230 (24.4)	78 (1.55)	70 (1.39)
Other	4 (0.06)	1 (25.0)	1 (25.0)	0 (0)	0 (0)
Smoking					
Never	3011 (42.2)	535 (17.8)	431 (14.3)	38 (1.26)	35 (1.16)
Ex-smoker	2238 (31.4)	702 (31.4)	621 (27.8)	35 (1.56)	33 (1.47)
Current Smoker	1321 (18.5)	471 (35.7)	424 (32.1)	32 (2.42)	16 (1.21)
Unknown	560 (7.85)	145 (25.9)	122 (21.8)	9 (1.61)	6 (1.07)
(b)	**Non-visible haematuria, n (%)**				
	Total patients	**All cancers**	**Bladder cancer**	**UTUC**	**Renal cancer**
Total	3152	201 (6.38)	165 (5.23)	9 (0.29)	13 (0.41)
Age					
<35	117 (3.71)	0	0 (0)	0 (0)	0 (0)
35–39	84 (2.67)	1 (1.19)	1 (1.19)	0 (0)	0 (0)
40–44	134 (4.25)	1 (0.75)	1 (0.75)	0 (0)	0 (0)
45–49	227 (7.20)	5 (2.20)	2 (0.88)	0 (0)	1 (0.44)
50–54	352 (11.2)	9 (2.56)	8 (2.27)	0 (0)	0 (0)
55–59	399 (12.7)	25 (6.27)	19 (4.76)	0 (0)	5 (1.25)
60–64	432 (13.7)	24 (5.56)	21 (4.86)	1 (0.23)	2 (0.46)
65–69	411 (13.0)	27 (6.57)	20 (4.87)	3 (0.73)	1 (0.24)
70–74	408 (13.0)	36 (8.82)	31 (7.60)	1 (0.25)	1 (0.25)
≥75	587 (18.6)	52 (12.4)	62 (10.6)	4 (0.68)	3 (0.51)
Sex					
Female	1770 (56.2)	54 (3.05)	46 (2.60)	4 (0.23)	5 (0.28)
Male	1380 (43.8)	147 (10.7)	119 (8.62)	5 (0.36)	8 (0.58)
Other	2 (0.06)	0 (0)	0 (0)	0 (0)	0 (0)
Smoking					
Never	1640 (52.0)	69 (4.21)	46 (2.80)	3 (0.18)	9 (0.55)
Ex-smoker	768 (24.4)	66 (8.59)	59 (7.68)	3 (0.39)	3 (0.39)
Current Smoker	560 (17.8)	50 (8.93)	47 (8.39)	3 (0.54)	1 (0.18)
Unknown	184 (5.84)	16 (8.70)	13 (7.07)	0 (0)	0 (0)

Percentages are row percentages (n/N patients), except for the first column ('Total patients') which are column percentages.

clinical trial for bladder cancer, so the observed prevalence is likely influenced by patient selection. Furthermore, their reference standard for upper tract cancer diagnosis was based solely on MDT meeting consensus after review of imaging. Conversely, we determined detailed cancer positive and negative classification from the offset and considered histopathological diagnosis, as well as the outcome of local MDT meetings, for each type of cancer. We also reported the proportion of cancer-positive cases determined by each of these (Table S5).

Other cohort studies have also reported lower bladder cancer rates of 10.3–11.9%, but these have been smaller single-centre retrospective studies [8,9]. These also lack transparency in their classification of disease outcome and smoking history was not recorded in the study by Edwards *et al.* [8]. Furthermore, the proportions of patients with VH and NVH in these studies were almost equal, reflecting a selected population. However, in our present study that is reflective of an international population, two-thirds of patients had VH, and so prevalence will be expectedly higher.

Table 3 Adjusted and unadjusted cancer prevalence estimates by type of haematuria and cancer.

Patient group	Cancer type	Unadjusted prevalence, % (95% CI)	Adjusted prevalence, % (95% CI)
All patients with haematuria	All cancers	20.0 (19.2–20.8)	28.2 (22.3–34.1)
	Bladder cancer	17.1 (16.4–17.9)	24.7 (19.1–30.2)
	UTUC	1.20 (1.00–1.43)	1.14 (0.77–1.52)
	Renal cancer	1.00 (0.83–1.21)	1.05 (0.80–1.29)
	Prostate cancer	1.79 (1.49–2.14)	1.75 (1.32–2.18)
Visible haematuria	All cancers	26.0 (25.0–27.0)	33.4 (26.7–40.0)
	Bladder cancer	22.4 (21.5–23.4)	29.3 (23.0–35.8)
	UTUC	1.60 (1.33–1.92)	1.47 (0.98–1.96)
	Renal cancer	1.26 (1.03–1.55)	1.27 (0.95–1.58)
	Prostate cancer	1.94 (1.60–2.36)	1.88 1.39–2.37)
Non-visible haematuria	All cancers	6.38 (5.58–7.28)	15.5 (10.8–20.2)
	Bladder cancer	5.23 (4.51–6.07)	13.1 (8.82–17.4)
	UTUC	0.29 (0.15–0.54)	0.36 (0.10–0.62)
	Renal cancer	0.41 (0.24–0.70)	0.50 (0.22–0.79)
	Prostate cancer	1.23 (0.77–1.96)	1.25 (0.56–1.93)

Prevalence was adjusted for sex, age, smoking status and country and centre effects using a mixed-effect multivariable logistic regression. For the analyses of all patients with haematuria, we also adjusted for type of haematuria. The total number of patients in the unadjusted analysis was 10 282 (the NH group was excluded in this analysis), and for the adjusted analysis was 9531, except when estimating prostate cancer prevalence where the total number of patients in the unadjusted analysis was 6429 and for the adjusted analysis was 5938.

Table 4 Association of risk markers with prevalence of urinary tract cancers using multivariable mixed-effects logistic regression.

	All cancers (1892/9531)		Bladder cancer (1629/9531)		UTUC (114/9531)		Renal cancer (97/9531)		Prostate cancer (101/5938)	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	1.04 (1.03–1.05)	<0.001	1.04 (1.03–1.05)	<0.001	1.04 (1.03–1.06)	<0.001	1.00 (0.98–1.01)	0.55	1.04 (1.03–1.06)	<0.001
Haematuria										
NVH	1.00		1.00		1.00		1.00		1.00	
VH	3.47 (2.90–4.15)	<0.001	3.50 (2.88–4.26)	<0.001	4.23 (2.09–8.55)	<0.001	2.56 (1.40–4.67)	<0.001	1.53 (0.85–2.74)	0.16
Sex										
Female	1.00		1.00		1.00		1.00		–	–
Male	1.30 (1.14–1.50)	<0.001	1.15 (1.00–1.34)	0.058	0.74 (0.49–1.11)	0.15	1.54 (0.95–2.49)	0.08	–	–
Smoking										
Never smoked	1.00		1.00		1.00		1.00		1.00	
Ex-smoker	1.85 (1.61–2.13)	<0.001	2.19 (1.88–2.55)	<0.001	1.14 (0.72–1.81)	0.57	1.11 (0.70–1.76)	0.44	0.53 (0.34–0.83)	0.005
Current smoker	2.70 (2.30–3.18)	<0.001	3.18 (2.67–3.78)	<0.001	2.49 (1.53–4.04)	<0.001	0.83 (0.47–1.47)	0.52	0.40 (0.20–0.79)	0.009
Random effects variance										
Country	0.64 (0.27–0.28)		0.67 (0.30–1.49)		0.04 (0.00–4.74)		0.00		0.00	
Centre	0.38 (0.08–0.25)		0.42 (0.28–0.64)		0.34 (0.08–1.40)		0.25 (0.05–1.21)		0.45 (0.17–1.23)	
Intraclass correlation										
Country	0.15 (0.07–28.3)		0.15 (0.07–28.8)		0.01 (0.00–0.58)		0.00		0.00	
Centre	0.27 (0.17–33.9)		0.25 (0.17–0.35)		0.10 (0.04–0.27)		0.07 (0.02–0.27)		0.12 (0.05–0.27)	

The unadjusted prevalence of bladder cancer (17.1%) was lower than the adjusted prevalence (24.7%). Country-specific cancer prevalence varied greatly, and the adjustment for country had the biggest effect on prevalence. We suspect the low unadjusted prevalence is due to a relatively low cancer prevalence in the largest contributing country (UK) compared to the rest of the cohort. Adjusting for this effect provided a more accurate estimate of prevalence. This highlights the likely underestimation of prevalence in previous studies where this adjustment has not been carried out, and the problem of single-centre studies when there is so much variation even within a country.

Patients referred with NH were included in the study to minimise selection bias and reflect clinical practice. The high proportion of pre-referral suspected abnormality on imaging explains the high 33.1% prevalence of cancer in this group. Clinicians should therefore have a high index of suspicion of urinary tract cancer in patients being referred following abnormal imaging. However, this group made up a small proportion (5.64%) of the cohort and further evaluation is warranted to shed light on potential factors that can improve the diagnostic efficiency of urinary tract cancer in patients with NH.

One limitation of the present study is generalisability to primary care populations. The study was conducted in secondary care and we are not aware of the effects of triage that occurred at a primary care level. Further limitations include any other unknown confounding variables associated with detection of cancer that we did not adjust for. We focussed on variables chosen *a priori* with biological plausibility for having an association with cancer detection.

Future work from the IDENTIFY study will focus on developing a cancer prediction model using key patient characteristics to risk-stratify patients, in addition to diagnostic test evaluation, to develop a patient-specific diagnostic algorithm for haematuria. It is hoped that by adopting such algorithms, patients with suspected urinary tract cancer may receive more tailored investigations based on their individual risk, which focus on the detection of cancers, whilst minimising unnecessary over-investigation. In addition, further evaluation of the IDENTIFY data will explore: the variation in prevalence between countries, the effect of different protocols for haematuria and different healthcare systems on cancer prevalence, the patient group with NH, the different grades of NVH, and the implication of different international referral guidelines on this cohort.

In conclusion, the present study provides a robust contemporary evaluation of cancer prevalence in patients referred to secondary care with suspected urinary tract cancer. Adjustment for patient risk markers and geographical variation resulted in more accurate cancer prevalence. Patients are commonly referred with VH, and bladder cancer is the most prevalent cancer.

Acknowledgements

We would like to thank all of the BURST research collaborators for taking part in this study and Jonathan Deeks for his support from the Test Evaluation Research Group. Veeru Kasivisvanathan is an Academic Clinical Lecturer funded by the UK National Institute for Health Research (NIHR). Yemisi Takwoingi is funded by a UK NIHR Postdoctoral Fellowship and supported by the NIHR Birmingham Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NHS, NIHR or the Department of Health and Social Care. Although unrelated to the present study, the BURST research collaborative would like to acknowledge funding from the *BJU International*, BAUS, Ferring Pharmaceuticals Ltd, and Dominvs Group.

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Disclosure of Interests

None of the authors or collaborators has disclosed any conflict of interest

Funding

Grants from Action Bladder Cancer UK, The Urology Foundation, The Rosetrees Trust were used for costs of statistical analysis and dissemination of results at international meetings and conferences. There were no endorsements from pharmaceutical companies or agencies to write this article. The corresponding author (Sinan Khadhouri) had full access to the data and held the final responsibility to submit the manuscript. Action Bladder Cancer UK, The Urology Foundation, The Rosetrees Trust.

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Appendix

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Abbreviations: BURST, British Urology Researchers in Surgical Training (Collaborative Group); IDENTIFY, Investigation and Detection of Urological Neoplasia in Patients Referred With Suspected Urinary Tract Cancer; MDT, multidisciplinary team; NH, no haematuria; NIHR, UK National Institute for Health Research; NVH, non-visible haematuria (microscopic or dipstick); OR, odds ratio; UTUC, upper tract urothelial cancer; VH, visible haematuria (macroscopic or gross).

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Cancer classification.
Table S2 Number of centres and patients observed in each participating country and unadjusted cancer prevalence stratified by type of haematuria.
Table S3 List of participating hospitals.
Table S4 Reasons for referral of patients with NH.
Table S5 Cancer outcome classification.
Appendix S1 Primary choice of imaging in patients presenting with VH and NVH according to hospital protocols of participating sites.