TITLE PAGE

The IDENTIFY Study: The Investigation and Detection of Urological Neoplasia in Patients Referred with Suspected Urinary Tract Cancer; A multicentre observational study

Author names and affiliations
(First name, Surname)

Sinan Khadhouri
University of Aberdeen, Health Services Research Unit, Aberdeen, UK
Aberdeen Royal Infirmary, Aberdeen, UK
British Urology Researchers in Surgical Training (BURST) Collaborative

Kevin M Gallagher
Department of Clinical Surgery
Western General Hospital
University of Edinburgh
Edinburgh, UK
British Urology Researchers in Surgical Training (BURST) Collaborative

Kenneth R MacKenzie
Freeman Hospital, Newcastle Upon Tyne, UK
British Urology Researchers in Surgical Training (BURST) Collaborative

Taimur T Shah
Charing Cross Hospital, Imperial College Healthcare NHS Trust, Dept. of Surgery and Cancer, London, UK

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/BJU.15483

Division of Surgery, Department of Surgery and Cancer, Imperial College London, London, UK.
British Urology Researchers in Surgical Training (BURST) Collaborative

Chuanyu Gao
Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
British Urology Researchers in Surgical Training (BURST) Collaborative

Sacha Moore
Wrexham Maelor Hospital, Wrexham, UK
British Urology Researchers in Surgical Training (BURST) Collaborative

Eleanor F Zimmermann
Torbay and South Devon NHS Foundation Trust, Torbay, UK
British Urology Researchers in Surgical Training (BURST) Collaborative

Eric Edison
Department of Urology, Whipps Cross Hospital, Barts Health NHS Trust, London, UK
British Urology Researchers in Surgical Training (BURST) Collaborative

Matthew Jefferies
Morriston Hospital, Swansea, UK
British Urology Researchers in Surgical Training (BURST) Collaborative

Arjun Nambiar
Freeman Hospital, Newcastle Upon Tyne, UK
British Urology Researchers in Surgical Training (BURST) Collaborative

Miles P. Mannas
Department of Urologic Sciences, University of British Columbia, Vancouver, Canada

Taeweon Lee
Department of Urologic Sciences, University of British Columbia, Vancouver, Canada

Giancarlo Marra
Department of Surgical Sciences, Città della Salute e della Scienza, Turin, Italy
University of Turin, Turin, Italy

Beatrice Lillaz
SanGiovanni Battista Hospital, Turin, Italy

Juan Gómez Rivas
Department of Urology, La Paz University Hospital, Madrid, Spain

Jonathan Olivier
Urology department, Claude Huriez Hospital, CHU Lille, F-59000 Lille, France

Mark A. Assmus
Division of Urology, Department of Surgery, University of Alberta, Edmonton, Alberta, Canada

Taha Uçar
Department of Urology, Istanbul Medeniyet University, Turkey

Francesco Claps
Urological Clinic, Department of Medicine, Surgery and Health Sciences, University of Trieste, Trieste, Italy

Matteo Boltri
Urological Clinic, Department of Medicine, Surgery and Health Sciences, University of Trieste, Trieste, Italy

Tara Burnhope
University Hospitals of Derby and Burton NHS Foundation Trust, Derby, UK

Nkwam Nkwam

University Hospitals of Derby and Burton NHS Foundation Trust, Derby, UK

George Tanasescu
Department of Urology, Queen Alexandra Hospital, Portsmouth, UK

Nicholas E Boxall
Salford Royal NHS Foundation Trust, Salford, UK

Alison P Downey
Doncaster Royal Infirmary, UK

Asim Ahmed Lal
University of North Carolina Hospitals, Chapel Hill, North Carolina, USA

Marta Antón-Juanilla
Department of Urology, Hospital Universitario Cruces, Barakaldo, Spain

Holly Clarke
Bradford Teaching Hospitals, NHS Foundation Trust, UK

David HW Lau
Aberdeen Royal Infirmary, Aberdeen, UK

Kathryn Gillams
Great Western Hospitals NHS Foundation Trust, Swindon, UK

Matthew Crockett
Frimley Renal Cancer Centre, Frimley Hospitals NHS Foundation Trust, UK

Matthew Nielsen
University of North Carolina Hospitals, Chapel Hill, North Carolina, USA

Yemisi Takwoingi
Test Evaluation Research Group, Institute of Applied Health Research, University of Birmingham, and NIHR Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust and University of Birmingham, UK

Naomi Chuchu
Test Evaluation Research Group, Institute of Applied Health Research, University of Birmingham, Birmingham, UK

John O'Rourke
Test Evaluation Research Group, Institute of Applied Health Research, University of Birmingham, Birmingham, UK

Graeme MacLennan
Health Services Research Unit, University of Aberdeen, Aberdeen, UK

John S McGrath
University of Exeter Medical School, Exeter, UK
Royal Devon and Exeter NHS Foundation Trust, Exeter, UK

Veeru Kasivisvanathan
University College London, Division of Surgery and Interventional Science, UK
University College London Hospitals NHS Foundation Trust, Dept. of Urology, London, UK
British Urology Researchers in Surgical Training (BURST) Collaborative

IDENTIFY Study group*

Contributors
SK and JM were responsible for the study idea. SK, VK and TT developed the concept. SK, KG, TT and VK were responsible for the study design. SK, KG and KM were responsible for coordinating the study. SK, KM, TT, CG, SM, EZ and EE were responsible for data quality assurance. YT, JOR and NC, KG and SK were involved in data cleaning and statistical analysis.

SK wrote the first draft of the manuscript with support from KG and VK. All mainline authors were involved in the interpretation, editing, critical review and final approval of the manuscript. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

***Pubmed indexed collaborators:**

Aasem Chaudry, Abhishek Sharma, Adam Bennett, Adnan Ahmad, Ahmed Abroaf, Ahmed Musa Suliman, Aimee Lloyd, Alastair McKay, Albert Wong, Alberto Silva, Alexandre Schneider, Alison MacKay, Allen Knight, Alkiviadis Grigorakis, Amar Bdesha, Amy Nagle, Ana Cebola, Ananda Kumar Dhanasekaran, Andraž Kondža, André Barcelos, Andrea Benedetto Galosi, Andrea Ebur, Andrea Minervini, Andrew Russell, Andrew Webb, Ángel García de Jalón, Ankit Desai, Anna Katarzyna Czech, Anna Mainwaring, Anthony Adimonye, Arighno Das, Arnaldo Figueiredo, Arnauld Villers, Artur Leminski, Arvinda Chippagiri, Asim Ahmed Lal, Asıf Yıldırım, Athanasios Marios Voulgaris, Audrey Uzan, Aye Moh Moh Oo, Ayman Younis, Bachar Zelhof, Bashir Mukhtar, Ben Ayres, Ben Challacombe, Benedict Sherwood, Benjamin Ristau, Billy Lai, Brechtje Nellensteijn, Brielle Schreiter, Carlo Trombetta, Catherine Dowling, Catherine Hobbs, Cayo Augusto Estigarribia Benitez, Cédric Lebacle, Cherrie Wing Yin Ho, Chi-Fai Ng, Chloe Mount, Chon Meng Lam, Chris Blick, Christian Brown, Christopher Gallegos, Claire Higgs, Clíodhna Browne, Conor McCann, Cristina Plaza Alonso, Daniel Beder, Daniel Cohen, Daniel Gordon, Daniel Wilby, Danny Gordon, David Hrouda, David Hua Wu Lau, Dávid Karsza, David Mak, David Martin-Way, Denula Suthaharan, Dhruv Patel, Diego M Carrion, Donald Nyanhongo, Edward Bass, Edward Mains, Edwin Chau, Elba Canelon Castillo, Elizabeth Day, Elsayed Desouky, Emily Gaines, Emma Papworth, Emrah Yuruk, Enes Kilic, Eoin Dinneen, Erika Palagonia, Evanguelos Xylinas, Faizan Khawaja, Fernando Cimarra, Florian Bardet, Francesca Kum, Francesca Peters, Gábor Kovács, Geroge Tanasescu, Giles Hellawell, Giovanni Tasso, Gitte Lam, Giuseppe La Montagna, Giuseppe Pizzuto, Gordan Lenart, Graeme MacLennan, Günal Özgür, Hai Bi, Hannah Lyons, Hannah Warren, Hashim Ahmed, Helen Simpson, Helena Burden, Helena Gresty, Hernado Rios Pita, Holly Clarke, Hosam Serag, Howard Kynaston, Hugh Crawford-Smith, Hugh Mostafid, Hugo Otaola-Arca, Hui Fen Koo, Ibrahim Ibrahim, Idir Ouzaid, Ignacio Puche-Sanz, Igor Tomašković, Ilker Tinay, Iqbal Sahibzada, Isaac Thangasamy, Iván Revelo Cadena, Jacques Irani, Jakub Udzik, James Brittain, James Catto, James Green, James

Tweedle, Jamie Borrego Hernando, Jamie Leask, Jas Kalsi, Jason Frankel, Jason Toniolo, Jay D. Raman, Jean Courcier, Jeevan Kumaradeevan, Jennifer Clark, Jennifer Jones, Jeremy Yuen-Chun Teoh, John Iacovou, John Kelly, John P Selph, Jonathan Aning, Jon Deeks, Jonathan Cobley, Jonathan Olivier, Jonny Maw, José Antonio Herranz-Yagüe, Jose Ignacio Nolazco, Jose Manuel Cózar-Olmo, Joseph Bagley, Joseph Jelski, Joseph Norris, Joseph Testa, Joshua Meeks, Juan Hernandez, Juan Luis Vásquez, Karen Randhawa, Karishma Dhera, Katarzyna Gronostaj, Kathleen Houlton, Kathleen Lehman, Kathryn Gillams, Kelvin Adasonla, Kevin Brown, Kevin Murtagh, Kiki Mistry, Kim Davenport, Kosuke Kitamura, Laura Derbyshire, Laurence Clarke, Lawrie Morton, Levin Martinez, Louise Goldsmith, Louise Paramore, Luc Cormier, Lucio Dell'Atti, Lucy Simmons, Luis Martinez-Piñeiro, Luis Rico, Luke Chan, Luke Forster, Lulin Ma, Madeline Moore, Maria Camacho Gallego, Maria José Freire, Mark Emberton, Mark Feneley, Marta Antón-Juanilla, Marta Viridiana Muñoz Rivero, Matea Pirša, Matteo Tallè, Matthew Crockett, Matthew Liew, Matthew Trail, Meghan Cooper, Meghana Kulkarni, Michael Ager, Ming He, Mo Li, Mohamed Omran Breish, Mohamed Tarin, Mohammed Aldiwani, Mudit Matanhelia, Muhammad Pasha, Mustafa Kaan Akalın, Nasreen Abdullah, Nathan Hale, Neha Gadiyar, Neil Kocher, Nicholas Bullock, Nicholas Campain, Nicola Pavan, Nihad Al-Ibraheem, Nikita Bhatt, Nishant Bedi, Nitin Shrotri, Niyati Lobo, Olga Balderas, Omar Kouli, Otakar Capoun, Pablo Oteo Manjavacas, Paolo Gontero, Paramananthan Mariappan, Patricio Garcia Marchiñena, Paul Erotocritou, Paul Sweeney, Paula Planelles, Peter Acher, Peter C. Black, Peter K Osei-Bonsu, Peter Østergren, Peter Smith, Peter-Paul Michiel Willemse, Piotr L. Chlosta, Qurrat Ul Ain, Rachel Barratt, Rachel Esler, Raihan Khalid, Ray Hsu, Remigiusz Stamirowski, Reshma Mangat, Ricardo Cruz, Ricky Ellis, Robert Adams, Robert Hessell, Robert J.A. Oomen, Robert McConkey, Robert Ritchie, Roberto Jarimba, Rohit Chahal, Rosado Mario Andres, Rosalyn Hawkins, Rotimi David, Rustom P Manecksha, Sachin Agrawal, Syed Sami Hamid, Samuel Deem, Sanchia Goonewardene, Satchi Kuchibhotla Swami, Satoshi Hori, Shahid Khan, Shakeel Mohammud Inder, Shanthi Sangaralingam, Shekhar Marathe, Sheliyan Raveenthiran, Shigeo Horie, Shomik Sengupta, Sian Parson, Sidney Parker, Simon Hawlina, Simon Williams, Simone Mazzoli, Slawomir Grzegorz Kata, Sofia Pinheiro Lopes, Sónia Ramos, Sonpreet Rai, Sophie Rintoul-Hoad, Sorcha O'Meara, Steve Morris, Stacey Turner, Stefano Venturini, Stephanos Almpanis, Steven Joniau, Sunjay Jain, Susan Mallett, Sven Nikles, Shahzad, Sylvia Yan, Taeweon Lee, Taha Uçar, Tamsin Drake, Tarq Toma, Teresa Cabañuz Plo, Thierry Bonnin, Tim Muilwijk, Tim Wollin, Timothy Shun Man CHU, Timson Appanna, Tom Brophy, Tom Ellul,

Tomas Austin, Tomaž Smrkolj, Tracey Rowe, Troy Sukhu, Trushar Patel, Tullika Garg, Turhan Çaşkurlu, Uros Bele, Usman Haroon, Víctor Crespo-Atín, Victor Parejo Cortes, Victoria Capapé Poves, Vincent Gnanapragasam, Vineet Gauhar, Vinnie During, Vivek Kumar, Vojtech Fiala, Wasim Mahmalji, Wayne Lam, Yew Fung Chin, Yigit Filtekin, Yih Chyn Phan, Youssed Ibrahim, Zachary A Glaser, Zainal Adwin Abiddin, Zijian Qin, Zsuzsanna Zotter, Zulkifli Zainuddin

Conflict of Interest

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

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 United Kingdom 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.

Though unrelated to this study, the BURST research collaborative would like to acknowledge funding from the BJU international, the British Association of Urological Surgeons, Ferring Pharmaceuticals Ltd and Dominvs Group.

Word Count

- Abstract: 271
- Manuscript = 2714

Funding statement

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 (SK) had full access to the data and held the final responsibility to submit the manuscript.

MR. SINAN KHADHOURI (Orcid ID : 0000-0002-1836-8992)
MR. KEVIN MICHAEL GALLAGHER (Orcid ID : 0000-0001-5485-5336)
DR. SACHA L MOORE (Orcid ID : 0000-0002-0914-2051)
DR. JUAN GÓMEZ RIVAS (Orcid ID : 0000-0002-0556-3035)
DR. JONATHAN OLIVIER (Orcid ID : 0000-0002-5409-2911)
DR. MARK ALEXANDER ASSMUS (Orcid ID : 0000-0003-3615-9251)
DR. FRANCESCO CLAPS (Orcid ID : 0000-0003-2812-5553)
MR. NKWAM NKWAM (Orcid ID : 0000-0003-1086-6388)
MR. JOHN MCGRATH (Orcid ID : 0000-0001-9416-9912)

Article type : Original Article

The IDENTIFY Study: The Investigation and Detection of Urological Neoplasia in Patients Referred with Suspected Urinary Tract Cancer; A multicentre observational study

ABSTRACT

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 and over, 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% CI 22.3–34.1), bladder cancer (n=1951) 24.7% (19.1–30.2), UTUC (n=128) 1.14% (0.77–1.52), renal cancer (n=107) 1.05% (0.80–1.29) and prostate cancer (n=124) 1.75% (1.32–2.18). 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 (2.90–4.15) p<0.0001, male sex 1.30 (1.14–1.50) p<0.001 and smoking 2.70 (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.

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 cell carcinoma (RCC) (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 and non-visible (microscopic or dipstick) haematuria. 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 visible haematuria (VH) compared to non-visible haematuria (NVH), and this is a known predictor of urinary tract cancer (7)(8)(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)(11)(12).

Cancer prevalence data can inform clinical guidelines on referral of patients for investigation of suspected urinary tract cancer, as demonstrated 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 nor 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, upper tract urothelial, renal 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 & setting

The IDENTIFY study was an international prospective cohort study conducted by the BURST (British Urology Researchers in Surgical Training) 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). Patient data were obtained from hospital records of consecutive patients attending a secondary care 'haematuria clinic' for a diagnostic cystoscopy between December 2017 to 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) (17).

Participants

We included patients aged 16 years or over, with or without haematuria, referred to a urologist for the investigation of suspected urinary tract cancer (defined as bladder, upper tract urothelial 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, upper tract urothelial, renal 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 in line 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, renal, upper tract urothelial and prostate cancer before analysis of prevalence (Supplementary table 1). Pathological definitions were based on the WHO cancer classification system (18)(19). Patients with histological or clinical evidence for cancer after multidisciplinary team 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 keeping 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, urinalysis, cytology, imaging findings, cystoscopy findings, histopathology from biopsies or surgery and multidisciplinary team 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. Non-visible haematuria was defined by a trace or more on urine dipstick, or over 3 red blood cells per 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% confidence interval 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). Confidence intervals (CI) were calculated using the Wilson method (21)(22). Patients with no haematuria (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 under 35 years to reflect the lowest age threshold used in international guidelines (3)(24). Five-year age bins 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, Texas, United States). A p value of less than 0.05 was deemed statistically significant.

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 in line 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 (Supplementary tables 2 and 3 details the number of patients and cancers in each country/site). Approximately two-thirds (65.4%) of patients were referred with VH and 28.9% with NVH (Figure 1). The remaining (5.64%) patients had no haematuria and reasons for their referral are given in Supplementary table 4.

Patient demographics and clinical characteristics are shown in Table 1. The cancer classifications are detailed in Supplementary table 5. Of the 10,896 patients, 2,257 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 0.99–1.39), 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 RCC) by type of haematuria for different age groups, sex and smoking status are shown in Table 2. 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 under 35-years-old, nor RCCs in under 40-year-olds or UTUCs in under 60-year-olds. In patients with VH, the overall cancer prevalence was 17.8% in never smokers versus 35.7% in current smokers and 19.9% in females versus 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, RCC and prostate cancer.

The multivariable mixed effects logistic regression used for adjustment, showed that visible haematuria, 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 (OR 3.50, 95% CI 2.88–4.26, p<0.0001), UTUC (OR 4.23, 95% CI 2.09–8.55, p<0.0001) and RCC (OR 2.56, 95% CI 1.40–4.67, p<0.0001). Increasing age (OR 1.04, 95% CI 1.03–1.06, p<0.0001) 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 (OR1.54, 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 RCC, accounted for approximately 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 under 35-years-old for bladder cancer or under 60-years-old 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 this 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 this 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 this 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 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 multidisciplinary team meeting consensus following 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 multidisciplinary team meetings for each type of cancer. We also reported the proportion of cancer positive cases determined by each of these (supplementary table 5).

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 proportion of patients with visible and non-visible haematuria in these studies were almost equal, reflecting a selected population. In our study that is reflective of an international population however, two-thirds of patients had visible haematuria, and so prevalence will be expectedly higher.

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 without haematuria 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 without haematuria.

One limitation of this 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 without haematuria, the different grades of NVH and the implication of different international referral guidelines on this cohort.

In conclusion, this 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 a more accurate cancer prevalence. Patients are commonly referred with VH, and bladder cancer is the most prevalent cancer.

Funding

Action Bladder Cancer UK, The Urology Foundation, The Rosetrees Trust

REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer [Internet]. 2018 Dec 6 [cited 2019 Aug 30];ijc.31937. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/ijc.31937
2. Wong MCS, Fung FDH, Leung C, Cheung WWL, Goggins WB, Ng CF. The global epidemiology of bladder cancer: a joinpoint regression analysis of its incidence and mortality trends and projection. Sci Rep [Internet]. 2018 Dec 18 [cited 2019 Aug 30];8(1):1129. Available from: http://www.nature.com/articles/s41598-018-19199-z
3. Tan WS, Feber A, Sarpong R, Khetrapal P, Rodney S, Jalil R, et al. Who Should Be Investigated for Haematuria? Results of a Contemporary Prospective Observational Study of 3556 Patients [Figure presented]. Eur Urol [Internet]. 2018;74(1):10–4. Available from: https://doi.org/10.1016/j.eururo.2018.03.008
4. Mathew A, Desai K. An Audit of Urology Two-Week Wait Referrals in a Large Teaching Hospital in England. Ann R Coll Surg Engl [Internet]. 2009 May [cited 2019 Aug 30];91(4):310. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19344552
5. Hawary AM, Warburton HE, Brough RJ, Collins GN, Brown SC, O'Reilly PH, et al.

The "2-week wait" rule for referrals for suspected urological cancers - Urgent need for refinement of criteria. Ann R Coll Surg Engl. 2008;90(6):517–22.

6. Rodgers MA, Hempel S, Aho T, Kelly JD, Kleijnen J, Westwood M. Diagnostic tests used in the investigation of adult haematuria: A systematic review. BJU Int. 2006;98(6):1154–60.
7. Price SJ, Shephard EA, Stapley SA, Barraclough K, Hamilton WT. Non-Visible Hematuria. Br J Gen. 2014;(September):584–9.
8. Edwards TJ, Dickinson AJ, Natale S, Gosling J, McGrath JS. A prospective analysis of the diagnostic yield resulting from the attendance of 4020 patients at a protocol-driven haematuria clinic. BJU Int. 2006;97(2):301–5.
9. Khadra MH, Pickard RS, Charlton M, Powell PH, Neal DE. A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice. J Urol. 2000;163(2):524–7.
10. Dobruch J, Daneshmand S, Fisch M, Lotan Y, Noon AP, Resnick MJ, et al. Gender and Bladder Cancer: A Collaborative Review of Etiology, Biology, and Outcomes. Eur Urol [Internet]. 2016 Feb 1 [cited 2019 Aug 30];69(2):300–10. Available from: https://www.sciencedirect.com/science/article/pii/S0302283815007824
11. Brennan P, Bogillot O, Cordier S, Greiser E, Schill W, Vineis P, et al. Cigarette smoking and bladder cancer in men: A pooled analysis of 11 case-control studies. Int J Cancer. 2000;86(2):289–94.
12. Schmidt-Hansen M, Berendse S, Hamilton W. The association between symptoms and bladder or renal tract cancer in primary care: A systematic review. Br J Gen Pract. 2015;65(640):e769–75.
13. Davis R, Jones JS, Barocas DA, Castle EP, Lang EK, Leveillee RJ, et al. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. J Urol [Internet]. 2012;188(6 SUPPL.):2473–81. Available from: http://dx.doi.org/10.1016/j.juro.2012.09.078
14. Gonzalez AN, Lipsky MJ, Li G, Rutman MP, Cooper KL, Weiner DM, et al. The Prevalence of Bladder Cancer During Cystoscopy for Asymptomatic Microscopic Hematuria. Urology. 2019;
15. Kasivisvanathan V, Ahmed H, Cashman S, Challacombe B, Emberton M, Gao C, et al. The British Urology Researchers in Surgical Training (BURST) Research Collaborative: an alternative research model for carrying out large scale multi-centre urological studies. BJU Int. 2018;121(1):6–9.

16. Khadhouri S, Gallagher KM, MacKenzie K, Shah TT, Gao C, Moore S, et al. IDENTIFY: The investigation and detection of urological neoplasia in patients referred with suspected urinary tract cancer: A multicentre cohort study. Int J Surg Protoc. 2020;21.
17. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;
18. Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs—Part A: Renal, Penile, and Testicular Tumours. Eur Urol. 2016;
19. Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs—Part B: Prostate and Bladder Tumours. Eur Urol. 2016;
20. Barocas DA, Boorjian SA, Alvarez RD, Downs TM, Gross CP, Hamilton BD, et al. Microhematuria: AUA/SUFU Guideline. J Urol. 2020;
21. Wilson EB. Probable Inference, the Law of Succession, and Statistical Inference. J Am Stat Assoc. 1927;
22. Brown LD, Cai TT, Das Gupta A. Interval estimation for a binomial proportion. Stat Sci. 2001;
23. Linder BJ, Bass EJ, Mostafid H, Boorjian SA. Guideline of guidelines: asymptomatic microscopic haematuria. BJU Int. 2018;121(2):176–83.
24. Rodney Davis, J. Stephen Jones, Daniel A. Barocas, Erik P. Castle, Erick K. Lang, Raymond J. Leveillee, Edward M. Messing, Scott D. Miller, Andrew C. Peterson, Thomas M.T. Turk WW. Microhematuria: Asymptomatic - American Urological Association [Internet]. AUA; 2016 [cited 2019 Nov 19]. Available from: https://www.auanet.org/guidelines/asymptomatic-microhematuria-(amh)-guideline

Table 1: Patient demographics and clinical characteristics

	Total n (%)	No cancer n (%)	All cancers n (%)	Bladder cancer n (%)	Upper tract urothelial cancer n (%)	Renal cancer n (%)	Prostate cancer n/total men (%)
Total	10896	8639 (79.3)	2257 (20.7)	1951 (17.9)	128 (1.17)	107 (0.98)	124/6807 (1.82)
Type of haematuria							
Non-visible haematuria	3152 (28.9)	2951 (34.2)	201 (8.91)	165 (8.46)	9 (7.03)	13 (12.1)	17 (13.7)
Visible haematuria	7130 (65.4)	5277 (61.1)	1853 (82.1)	1598 (81.9)	114 (89.1)	90 (84.1)	98 (79.0)
No haematuria	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)
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/total number of patients 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)							
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 [a]							
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 [b]							
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)
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)

Percentages are column percentages except in the first row ('Total'), which are row percentages.
[a] defined as exposure to dyes, rubber, textiles, pesticides [b] e.g. cyclophosphamide, pioglitazone. NA= Not applicable. UTI = Urinary Tract Infection. WCC = White cell count

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

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

Current Smoker	1321 (18.5)	471 (35.7)	424 (32.1)	32 (2.42)	16 (1.21)	560 (17.8)	50 (8.93)	47 (8.39)	3 (0.54)	1 (0.18)
Unknown	560 (7.85)	145 (25.9)	122 (21.8)	9 (1.61)	6 (1.07)	184 (5.84)	16 (8.70)	13 (7.07)	0 (0)	0 (0)

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

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)
	Upper tract urothelial cancer	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)
	Upper tract urothelial cancer	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)
	Upper tract urothelial cancer	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 analyses of all patients with haematuria, we also adjusted for type of haematuria. The total number of patients in the unadjusted analysis was 10282 (the no haematuria 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.

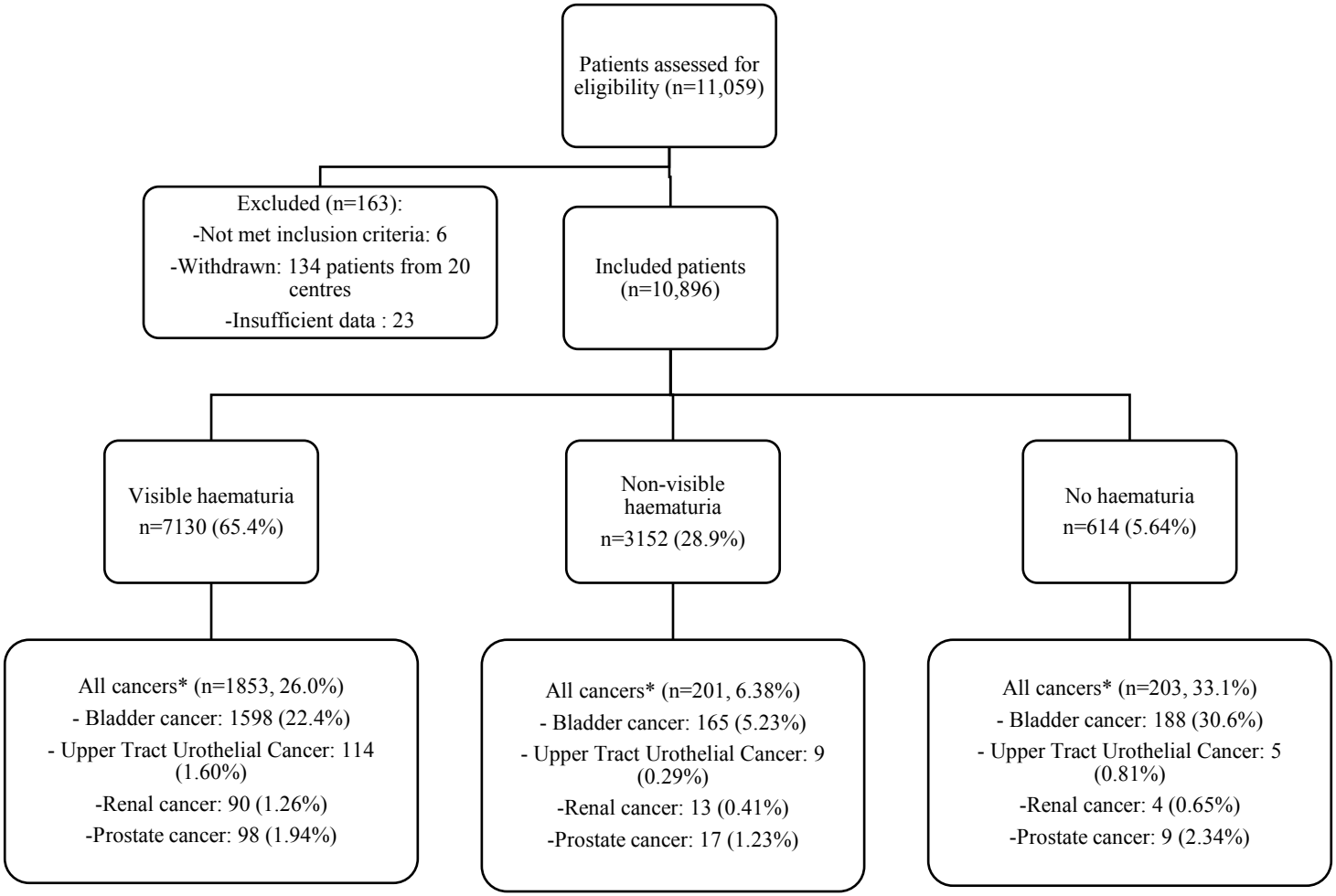
Table 4: Association of risk markers with prevalence of urinary tract cancers using multivariable mixed effects logistic regression

CI = Confidence Interval

	All cancers (1892/9531)		Bladder cancer (1629/9531)		Upper tract urothelial cancer (114/9531		Renal cancer (97/9531)		Prostate cancer 101/5938)	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Age	1.04 (1.03 –1.05)	<0.0001	1.04 (1.03 – 1.05)	<0.0001	1.04 (1.03 – 1.06)	<0.0001	1.00 (0.98 – 1.01)	0.55	1.04 (1.03 – 1.06)	<0.0001
Haematuria										
Non-visible	1.00		1.00		1.00		1.00		1.00	
Visible	3.47 (2.90 – 4.15)	<0.0001	3.50 (2.88 – 4.26)	<0.0001	4.23 (2.09 – 8.55)	<0.0001	2.56 (1.40 – 4.67)	<0.0001	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)	<0.0001	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)	<0.0001	2.19 (1.88 – 2.55)	<0.0001	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)	<0.0001	3.18 (2.67 – 3.78)	<0.0001	2.49 (1.53 – 4.04)	<0.0001	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)

Figure 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.