# Prevalence of urinary tract cancer in the Spanish cohort of the IDENTIFY study

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## Abstract

*Introduction:* Malignant tumors of the urinary tract are associated with high morbidity and mortality, and their prevalence can vary worldwide. Recently, the IDENTIFY study has published results on the prevalence of urinary tract cancer at a global level. This study evaluates the prevalence of cancer within the Spanish cohort of the IDENTIFY study to determine whether the published results can be extrapolated to our population.

*Patients and methods:* An analysis of the data from the Spanish cohort of patients in the IDEN-TIFY study was performed. This is a prospective cohort of patients referred to secondary care with suspected cancer, predominantly due to hematuria. Patients were recruited between December 2017 and December 2018.

*Results:* A total of 706 patients from 9 Spanish centers were analyzed. Of these, 277 (39.2%) were diagnosed with cancer: 259 (36.7%) bladder cancer, 10 (1.4%) upper tract urothelial carcinoma, 9 (1.2%) renal cancer and 5 (0.7%) prostate cancer. Increasing age (OR 1.05 (95% CI 1.03−1.06; $P < 0.001$)), visible hematuria (VH) OR 2.19 (95% CI 1.13−4.24; $P = 0.02$)) and smoking (ex-smokers: OR 2.11(95% CI 1.30−3.40; $P = 0.002$); smokers: OR 2.36 (95% CI 1.40−3.95; $P = 0.001$)) were associated with higher probability of bladder cancer.

*Conclusion:* This study highlights the risk of bladder cancer in patients with VH and smoking habits. Bladder cancer presented the highest prevalence; higher than the prevalence reported in previous series and presented in the IDENTIFY study. Future work should evaluate other associated factors that allow us to create cancer prediction models to improve the detection of cancer in our patients.

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## Prevalencia del cáncer del tracto urinario. Análisis de la cohorte española del estudio IDENTIFY

### Resumen

*Introducción:* Los tumores malignos del tracto urinario están asociados a gran morbilidad y mortalidad siendo su prevalencia variable a nivel global. Recientemente el estudio IDENTIFY ha publicado resultados sobre la prevalencia del cáncer del tracto urinario a nivel internacional. Este estudio evalúa la prevalencia de cáncer dentro de la cohorte española del estudio IDENTIFY para determinar si los resultados publicados son extrapolables a nuestra población.

*Material y métodos:* Se realizo un análisis de los datos de la cohorte de pacientes españoles del estudio IDENTIFY. Se trata de una cohorte prospectiva de pacientes derivados al hospital con sospecha de cáncer, predominantemente por hematuria. Los pacientes fueron reclutados entre diciembre de 2017 y diciembre de 2018.

*Resultados:* En total 706 pacientes procedente de 9 centros españoles fueron analizados. 277(39,2%) fueron diagnosticados de cáncer, 259(36.7%) cáncer vejiga, 10(1.4%) tracto urinario superior, 9 (1.2%) renal y 5 (0.7%) próstata. El aumento de la edad (OR 1,05(95%CI 1,03−1,06;<0,001)), presencia de hematuria visible OR 2,19(95%CI1,13−4,24;P = 0,02)) y el hábito tabáquico (exfumadores:OR2,11(95%CI1,30−3,40;P = 0,002); fumadores:OR2,36(95%CI 1,40−3,95;P = 0,001)) se asocia con mayor probabilidad de cáncer vesical.

*Conclusión:* Este estudio resalta el riesgo que existe en pacientes con HV y habito tabáquico de presentar cáncer de vejiga. El cáncer de vejiga presentó la mayor prevalencia, siendo esta mayor que la expuesta en series previas y la presentada en el estudio IDENTIFY. Trabajos futuros deben evaluar otros factores asociados que permitan crear modelos de predicción de cáncer para seguir aumentando la detección de estos en nuestros pacientes.

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## Introduction

Malignant tumors of the urinary tract are associated with high morbidity and mortality, but their prevalence varies geographically.[1] The prevalence of bladder cancer (BC) is much higher compared to upper tract urothelial carcinoma (UTUC) and kidney cancer.[1,2] On the other hand, prostate cancer is the most frequently diagnosed urological tumor,[3] but it is usually presented and diagnosed through different routes than the previously mentioned tumors.[4]

Urinary tract tumors can evolve asymptomatically, with hematuria (macro or microscopic) as the most frequent symptom.[5] Visible (VH) or macroscopic hematuria is visible to the naked eye,[6] while non-visible (NVH) or microscopic hematuria requires urinalysis for diagnosis (≥3 red blood cells per high-power field).[7] There is a strong relationship between the diagnostic methods requested for the study of VH and NVH, since numerous pathologies can have both presentations.

In patients with hematuria, it is essential to diagnose those cases with a possible neoplasm. VH may be due to an underlying malignancy in 10−40%[8] of cases, while in NVH this percentage is 4.3%.[7,9]

Knowing the prevalence of urinary tract cancer in patients with hematuria helps to improve and generate new diagnostic algorithms.[10] Previous studies are based on systematic reviews or retrospective cohorts of data obtained at hospital level, and some of these are based on small samples and limited to specific geographical areas.[11−13] Most are prevalence estimates without adjustment for known risk markers or geographical variations detectable by multicenter studies.[14]

Recently, the IDENTIFY study has published results on the prevalence of urinary tract cancer.[14] It is the largest prospective analysis performed on patients referred with suspected urinary tract cancer worldwide. Thanks to the initial prevalence analysis, the IDENTIFY study group has been able to develop a risk calculator to classify patients.[15] The authors identified common and specific risk factors. The common factors were type of hematuria, age, sex, smoking history, high-risk occupation, travel, anticoagulation, and previous hematuria investigations.[15]

The prevalence of cancer varies between and within countries,[16] as observed in two of the studies of the IDENTIFY group. The English cohort had an overall cancer prevalence of 12.2%, while the international cohort had an overall can-

cer prevalence of 20.7%.[12,14] This difference points out the importance of analyzing the Spanish cohort to obtain information specific to the Spanish context.

The main objective of the study is to evaluate the prevalence of bladder, UTUC, kidney and prostate cancer in patients referred to the hospital with suspected cancer. The secondary objective is to evaluate the prevalence according to type of hematuria (VH, NVH), age group, sex, and smoking habits, and to evaluate the adjusted prevalence of cancer.

## Patients and methods

An analysis of the Spanish cohort of the IDENTIFY study was performed. The IDENTIFY study analyzed a prospective cohort of patients referred to secondary care with suspected cancer mainly due to hematuria. Patients were recruited between December 2017 and December 2018. The diagnosis was completed to rule out or confirm the presence of cancer. The study was closed in February 2019. The full study protocol, conducted by the British Urology Researchers in Surgical Training (BURST) Collaborative Group, is published with open access.[12] IDENTIFY has the approval of the local ethics committee of all participating hospitals. A complete list of the centers participating in the IDENTIFY study is attached in Appendix A.

### Participants

We included patients aged ≥16 years, with hematuria or with no hematuria (NH), referred to a urologist for the investigation of suspected urinary tract cancer (bladder cancer, UTUC or renal cancer). Patients were excluded if they had a previous diagnosis of urinary tract cancer or were undergoing investigations for recurrence. The collection of Spanish data was carried out in 9 centers, the complete list is included in Appendix B.

### Outcomes

The primary outcome was the prevalence of all cancers (bladder, UTUC, renal and prostate). The secondary outcomes were the prevalence of these cancers in patients according to type of hematuria and their association with age group, sex and smoking status. Prostate cancer was not included within the definition of patients referred with suspected urinary tract cancer because it usually follows different diagnostic pathways. Its prevalence is reported to maintain comparability with previous IDENTIFY studies.[14]

### Diagnostic criteria

For the calculation of prevalence, patients were classified as being cancer positive or cancer negative. Pathological criteria were based on the WHO cancer classification system and clinical definitions were based on the results of diagnostic tests, mainly imaging tests. Patients with histological or clinical evidence for cancer after multidisciplinary team (MDT) review were classified as cancer positive, whilst those without evidence of malignancy were classified as can-

cer negative. Applied diagnostic criteria were in accordance with current clinical practice.

### Data collection

Data were collected from medical records. These included the reason for referral, demographic information, urine analysis, cytology, imaging findings, cystoscopy findings, histopathology and MDT decisions. Type of hematuria was determined by the primary care referral letter, physical evaluation and patient's history. NVH was defined after confirmation on urine dipstick and VH was established in cases with macroscopic hematuria. On the other hand, NH patients were those referred with suspected cancer (mainly in imaging tests, but also due to lower urinary tract symptoms, repeat infections or cytology alterations) but without hematuria. Smoking status was categorized into current smoker, ex-smoker, and never smoked. All data recorded in the IDENTIFY database were verified for their complete and correct collection.

### Statistical analysis

Unadjusted estimates of cancer prevalence were calculated, obtaining their confidence intervals by using the Wilson method. Within each type of hematuria (VH and NVH), prevalence was stratified by age, sex, and smoking. We established <35 years as the lowest age threshold and used bins of 5 years according to current guideline recommendations.[17,18] As most of the patients referred without hematuria had already been incidentally diagnosed with some type of cancer and referred for confirmation, they were excluded from the analysis for the secondary objectives.

A mixed-effects logistic regression model was used to obtain adjusted prevalence. Risk markers were established on basis of prior evidence and plausibility for association with each type of cancer (type of hematuria, age, sex, and smoking status). The center was also included as a possible random effect in the variation in prevalence. Age was established as a continuous variable.

All analyses were performed using Stata version 16.1 1 (StataCorp, College Station, TX, USA), establishing a $p < 0.05$ as significant.

### Results

A total of 706 patients from the Spanish cohort were analyzed. All of them met the inclusion criteria and came from 9 Spanish centers.

Table 1 presents the demographic characteristics of the patients included for analysis. The mean age of the patients was 67 years, 77.8% male and not obese (42.9%). Regarding smoking habits, 37.3% were ex-smokers and 25.2% were current smokers. Of these, more than 43% had a significant smoking burden with a pack-year index >20.

The most common reason for referral was hematuria, mainly VH (83.7%) but also NVH (10.2%). Only 6.1% were referred without hematuria (NH), and 9.2% of all the

**Table 1** Patient demographics and clinical characteristics of the Spanish cohort, according to the presence or absence of cancer, and type of cancer.

| | Total, n (%) | No cancer, n (%) | All cancers, n (%) | Bladder cancer, n (%) | UTUC, n (%) | Renal cancer, n (%) | Prostate cancer, n (%) |
|---|---|---|---|---|---|---|---|
| Total | 706 | 429 (60.76%) | 277 (39.24%) | 259(36.69%) | 10 (1.42%) | 9 (1.27%) | 5 (0.71%) |
| Type of hematuria | | | | | | | |
| NVH | 72 (10.2%) | 57 (13.29%) | 15 (5.42%) | 13 (5.02%) | 1 (10.00%) | 1 (11.11%) | 0 (0%) |
| VH | 591 (83.71%) | 357 (83.22%) | 234 (84.48%) | 218 (84.17%) | 9 (90.00%) | 8 (88.89%) | 5 (100%) |
| NH | 43 (6.09%) | 15 (3.50%) | 28 (10.11%) | 28 (10.81%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Age, years | | | | | | | |
| Mean (SD) | 66.99 (0.49) | 64.46 (0.66) | 70.9 (0.69) | 70.8 (0.71) | 73.4 (2.28) | 68.67 (5.34) | 70.4 (3.47) |
| <35 | 14 (1.98%) | 12 (2.80%) | 2 (0.72%) | 2 (0.77%) | 0 (0%) | 0 (0%) | 0 (0%) |
| 35–39 | 12 (1.7%) | 12 (2.80%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| 40–44 | 11 (1.56%) | 10 (2.33%) | 1 (0.36%) | 1 (0.39%) | 0 (0%) | 0 (0%) | 0 (0%) |
| 45–49 | 26 (3.68%) | 22 (5.13%) | 4 (1.44%) | 3 (1.16%) | 0 (0%) | 1 (11.11%) | 0 (0%) |
| 50–54 | 42 (5.95%) | 26 (6.06%) | 16 (5.78%) | 14 (5.41%) | 0 (0%) | 2 (22.22%) | 0 (0%) |
| 55–59 | 76 (10.76%) | 60 (13.99%) | 16 (5.78%) | 16 (6.18%) | 0 (0%) | 0 (0%) | 0 (0%) |
| 60–64 | 100 (14.16%) | 61 (14.22%) | 39 (14.08%) | 38 (14.67%) | 1 (10%) | 1 (11.11%) | 1 (20%) |
| 65–69 | 116 (16.43%) | 67 (15.62%) | 49 (17.69%) | 47 (18.15%) | 2 (20%) | 0 (0%) | 2 (40%) |
| 70–74 | 88 (12.46%) | 52 (12.12%) | 36 (13.00%) | 34 (13.13%) | 2 (20%) | 1 (11.11%) | 1 (20%) |
| ≥75 | 221 (31.3%) | 107 (24.94%) | 114 (41.16%) | 104 (40.15%) | 5 (50%) | 4 (44.44%) | 1 (20%) |
| Sex | | | | | | | |
| Female | 156 (22.1%) | 106 (24.71%) | 50 (18.05%) | 45 (17.37%) | 3 (30.00%) | 3 (33.33%) | 0 (0%) |
| Male | 549 (77.76%) | 323 (75.29%) | 226 (81.59%) | 213 (82.24%) | 7 (70.00%) | 6 (66.67%) | 5 (100%) |
| Oher | 1 (0.14%) | 0 (0%) | 1 (0.36%) | 1 (0.39%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Smoking | | | | | | | |
| Never smoked | 192 (27.2 %) | 140 (32.63%) | 52 (18.77%) | 46 (17.76%) | 2 (20%) | 5 (55.56%) | 2 (40%) |
| Ex-smoker | 263 (37.25 %) | 135 (31.47%) | 128 (46.21%) | 122 (47.10%) | 6 (60%) | 1 (11.11%) | 2 (40%) |
| Current smoker | 178 (25.21 %) | 107 (24.94%) | 71 (25.63%) | 68 (26.25%) | 2 (20%) | 1 (11.11%) | 0 (0%) |
| Unknown | 73 (10.34 %) | 47 (10.96%) | 26 (9.39%) | 23 (8.88%) | 0 (0%) | 2 (22.22%) | 1 (20%) |
| Smoking index (n = 363) | | | | | | | |
| 0–10 | 54 (14.88 %) | 35 (20.00%) | 19 (10.11%) | 18 (10.06%) | 0 (0%) | 1 (50%) | 0 (0%) |
| 11–20 | 102 (28.1 %) | 62 (35.43%) | 40 (21.28%) | 37 (20.67%) | 3 (37.5%) | 0 (0%) | 0 (0%) |
| >20 | 156 (42.98 %) | 52 (29.71%) | 104 (55.32%) | 101 (56.42%) | 3 (37.5%) | 1 (50%) | 2 (100%) |
| Unknown | 51 (14.05 %) | 26 (14.86%) | 25 (13.30%) | 23 (12.85%) | 2 (25%) | 0 (0%) | 0 (0%) |
| UTI history | | | | | | | |
| None | 491 (69.55 %) | 254 (59.21%) | 237 (85.56%) | 220 (84.94%) | 9 (90%) | 8 (88.89%) | 5 (100%) |
| Single | 61 (8.64 %) | 48 (11.19%) | 13 (4.69%) | 13 (5.02%) | 1 (10%) | 0 (0%) | 0 (0%) |
| Recurrent | 46 (6.52 %) | 37 (8.62%) | 9 (3.25%) | 8 (3.09%) | 0 (0%) | 1 (11.11%) | 0 (0%) |
| Unknown | 108 (15.3 %) | 90 (20.98%) | 18 (6.50%) | 18 (6.95%) | 0 (0%) | 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 (%) |
|---|---|---|---|---|---|---|---|
| UTI at time of hematuria | | | | | | | |
| n/N with UTI (%) | 47/107 (0.44%) | 37/85 (43.53%) | 10/22 (45.45%) | 9/21 (42.86%) | 0/1 (0%) | 1/1 (100%) | 0/0 (NA) |
| Body mass index (BMI), kg/m$^2$ | | | | | | | |
| Mean (DS) | 26.83 (0.24) | 26.31 (0.32) | 27.34 (0.35) | 27.44 (0.37) | 25.63 (1.46) | 25.76 (1.6) | 26.42 (1.48%) |
| Not obese(BMI < 30) | 303 (42.92 %) | 158 (36.83%) | 145 (52.35%) | 133 (51.35%) | 8 (80%) | 6 (66.67%) | 4 (80%) |
| Obese (BMI ≥ 30) | 85 (12.04 %) | 36 (8.39%) | 49 (17.69%) | 45 (17.37%) | 2 (20%) | 1 (11.11%) | 1 (20%) |
| Missing | 318 (45.04 %) | 235 (54.78%) | 83 (29.96%) | 81 (31.27%) | 0 (0%) | 2 (22.22%) | 0 (0%) |
| Ethnicity | | | | | | | |
| White | 659 (93.34 %) | 393 (91.61%) | 266 (96.03%) | 248 (95.75%) | 10 (100%) | 9 (100%) | 5 (100%) |
| Asian | 3 (0.42 %) | 3 (0.70%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Black | 7 (0.99 %) | 4 (0.93%) | 3 (1.08%) | 3 (1.16%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Other | 14 (1.98 %) | 11 (2.56%) | 3 (1.08%) | 3 (1.16%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Missing | 23 (3.26 %) | 18 (4.20%) | 5 (1.81%) | 5 (1.93%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Occupational risk | | | | | | | |
| No | 473 (67 %) | 262 (61.07%) | 211 (76.17%) | 194 (74.90%) | 9 (90%) | 9 (100%) | 2 (40%) |
| Yes | 25 (3.54 %) | 12 (2.80%) | 13 (4.69%) | 12 (4.63%) | 1 (10%) | 0 (0%) | 3 (60%) |
| Unknown | 99 (14.02 %) | 64 (14.92%) | 35 (12.64%) | 35 (13.51%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Missing | 109 (15.44 %) | 91 (21.21%) | 18 (6.50%) | 18 (6.95%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Medication risk | | | | | | | |
| No | 554 (78.47 %) | 314 (73.19%) | 240 (86.64%) | 222 (85.71%) | 10 (100%) | 9 (100%) | 5 (100%) |
| Si | 5 (0.71 %) | 2 (0.47%) | 3 (1.08%) | 3 (1.16%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Unknown | 35 (4.96 %) | 21 (4.90%) | 14 (5.05%) | 14 (5.41%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Missing | 112 (15.86 %) | 92 (21.45%) | 20 (7.22%) | 20 (7.72%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Dysuria | | | | | | | |
| No | 603 (85.41 %) | 363 (84.62%) | 240 (86.64%) | 225 (86.87%) | 9 (90%) | 7 (77.78%) | 5 (100%) |
| Yes | i103 (14.59 %) | 66 (15.38%) | 37 (13.36%) | 34 (13.13%) | 1 (10%) | 2 (22.22%) | 0 (0%) |
| Raised WCC | | | | | | | |
| No | 338 (47.88 %) | 176 (41.03%) | 162 (58.48%) | 151 (58.30%) | 6 (60%) | 5 (55.56%) | 5 (100%) |
| Yes | 368 (52.12 %) | 253 (58.97%) | 115 (41.52%) | 108 (41.70%) | 4 (40%) | 4 (44.44%) | 0 (0%) |
| Previous hematuria evaluation | | | | | | | |
| No | 546 (77.34 %) | 298 (69.46%) | 248 (89.53%) | 230 (88.80%) | 10 (100%) | 9 (100%) | 5 (100%) |
| Yes | 65 (9.21 %) | 51 (11.89%) | 14 (5.05%) | 14 (5.41%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Missing | 95 (13.46 %) | 80 (18.65%) | 15 (5.42%) | 15 (5.79%) | 0 (0%) | 0 (0%) | 0 (0%) |

**Table 2** Proportion of cancers according to age, sex and smoking habits, stratified by type of hematuria.

| (a) | Visible hematuria, n (%) | | | | |
|-----|----------------|------------|----------------|------|-------------|
| | Total patients | All cancers | Bladder cancer | UTUC | Renal cancer |
| Total | 591 | 234 (39.59%) | 218 (36.89%) | 9 (1.52%) | 8 (1.35%) |
| **Age** | | | | | |
| <35 | 10 (1.69%) | 1 (0.43%) | 1 (0.46%) | 0 (0.00%) | 0 (0.00%) |
| 35–39 | 7 (1.18%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| 40–44 | 8 (1.35%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| 45–49 | 21 (3.55%) | 3 (1.28%) | 2 (0.92%) | 0 (0.00%) | 1 (12.50%) |
| 50–54 | 31 (5.25%) | 13 (5.56%) | 11 (5.05%) | 0 (0.00%) | 2 (25.00%) |
| 55–59 | 59 (9.98%) | 12 (5.13%) | 12 (5.50%) | 0 (0.00%) | 0 (0.00%) |
| 60–64 | 83 (14.04%) | 34 (14.53%) | 33 (15.14%) | 1 (11.11%) | 1 (12.50%) |
| 65–69 | 99 (16.75%) | 41 (17.52%) | 39 (17.89%) | 2 (22.22%) | 0 (0.00%) |
| 70–74 | 79 (13.37%) | 33 (14.10%) | 32 (14.68%) | 2 (22.22%) | 0 (0.00%) |
| ≥75 | 194 (32.83%) | 97 (41.45%) | 88 (40.37%) | 4 (44.44%) | 4 (50.00%) |
| **Sex** | | | | | |
| Female | 111 (18.78%) | 43 (18.38%) | 38 (17.43%) | 3 (33.33%) | 3 (37.50%) |
| Male | 480 (81.22%) | 191 (81.62%) | 180 (82.57%) | 6 (66.67%) | 5 (62.50%) |
| Other | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| **Smoking** | | | | | |
| Never | 158 (26.73%) | 46 (19.66%) | 41 (18.81%) | 2 (22.22%) | 4 (50.00%) |
| Ex-smoker | 221 (37.39%) | 105 (44.87%) | 100 (45.87%) | 5 (55.56%) | 1 (12.50%) |
| Current smoker | 146 (24.70%) | 59 (25.21%) | 56 (25.69%) | 2 (22.22%) | 1 (12.50%) |
| Unknown | 66 (11.17%) | 24 (10.26%) | 21 (9.63%) | 0 (0.00%) | 2 (25.00%) |

| (b) | Non-visible hematuria, n (%) | | | | |
|-----|----------------|------------|----------------|------|-------------|
| | Total patients | All cancers | Bladder cancer | UTUC | Renal cancer |
| Total | 72 | 15 (20.83%) | 13 (18.06%) | 1 (1.39%) | 1 (1.39%) |
| Age | | | | | |
| <35 | 2 (2.78%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| 35–39 | 5 (6.94%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| 40–44 | 2 (2.78%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| 45–49 | 4 (5.56%) | 1 (6.67%) | 1 (7.69%) | 0 (0.00%) | 0 (0.00%) |
| 50–54 | 9 (12.50%) | 1 (6.67%) | 1 (7.69%) | 0 (0.00%) | 0 (0.00%) |
| 55–59 | 13 (18.06%) | 2 (13.33%) | 2 (15.38%) | 0 (0.00%) | 0 (0.00%) |
| 60–64 | 11 (15.28%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| 65–69 | 12 (16.67%) | 4 (26.67%) | 4 (30.77%) | 0 (0.00%) | 0 (0.00%) |
| 70–74 | 5 (6.94%) | 1 (6.67%) | 0 (0.00%) | 0 (0.00%) | 1 (100%) |
| ≥75 | 9 (12.50%) | 6 (40.00%) | 5 (38.46%) | 1 (100%) | 0 (0.00%) |
| Sex | | | | | |
| Female | 31 (43.06%) | 1 (6.67%) | 1 (7.69%) | 0 (0.00%) | 0 (0.00%) |
| Male | 41 (56.94%) | 14 (93.33%) | 12 (92.31%) | 1 (100.00%) | 1 (100.00%) |
| Other | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) |
| Smoking | | | | | |
| Never | 26 (36.11%) | 3 (20.00%) | 2 (15.38%) | 0 (0.00%) | 1 (100.00%) |
| Ex-smoker | 14 (19.44%) | 5 (33.33%) | 4 (30.77%) | 1 (100.00%) | 0 (0.00%) |
| Current smoker | 26 (36.11%) | 6 (40.00%) | 6 (46.15%) | 0 (0.00%) | 0 (0.00%) |
| Unknown | 6 (8.33%) | 1 (6.67%) | 1 (7.69%) | 0 (0.00%) | 0 (0.00%) |

patients analyzed had undergone a prior hematuria investigation.

In total, 277 (39.2%) patients were diagnosed with cancer, 259 (36.7%) BC, 10 (1.4%) with UTUC, 9 (1.2%) with renal cancer and 5 (0.7%) with prostate cancer.

Table 2 shows the proportion of cancers according to age, sex and smoking, stratified by type of hematuria. Of the 591 patients referred with VH, 234 (39.6%) were diag-

nosed with cancer, and of the 72 patients with NVH, 15 (20.8%) were diagnosed with cancer. The most frequently diagnosed cancer in both groups was BC with 218 patients in the VH group (36.9%) and 13 in NVH (18.1%). To a lesser extent, UTUC was diagnosed in 9 patients (1.5%) and renal cancer in 8 patients (1.3%) in the VH group, and only 1 case of UTUC (1.4%) and 1 renal cancer (1.4%) in the NVH group.

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

| Patient group | Cancer type | Unadjusted prevalence %(95% CI) | Adjusted prevalence, % (95% CI)[a] |
|---|---|---|---|
| All patients with hematuria | All cancers | 37.56 (33.87—41.24) | 32.68 (24.90—41.54) |
| | Bladder cancer | 34.84 (31.21—38.47) | 30.17 (23.18—38.23) |
| | UTUC | 1.51 (0.58—2.44) | 0.22 (0.00—100.00) |
| | Renal cancer | 1.36 (0.48—2.24) | 0.94 (0.38—2.31) |
| | Prostate cancer | 0.96 (0.12—1.80) | 0 (0.00—100.00) |
| Visible hematuria | All cancers | 39.59 (35.65—43.54) | 35.77 (27.65—44.91) |
| | Bladder cancer | 36.89 (33.00—40.78) | 33.24 (25.89—41.50) |
| | UTUC | 1.52 (0.54—2.51) | 0.17 (0.00—100.00) |
| | Renal cancer | 1.35 (0.42—2.29) | 0.96 (0.37—2.43) |
| | Prostate cancer | 1.04 (0.13—1.95) | 0 (0.00—100.00) |
| Non-visible hematuria | All cancers | 21.13 (11.63—30.62) | 8.79 (2.89—23.79) |
| | Bladder cancer | 18.31 (9.31—27.31) | 8.34 (2.35—25.78) |
| | UTUC | 1.41 (0.00—4.15) | 0 (0.00—100.00) |
| | Renal cancer | 1.41 (0.00—4.15) | 0 (0.00—100.00) |
| | Prostate cancer | 0.00 (0.00—0.00) | 0.00 (0.00—0.00) |

a Prevalence was adjusted for sex, age, smoking status and country and center effects using a mixed-effect multivariable logistic regression. For the analyses of all patients with hematuria, we also adjusted for type of hematuria. The total number of patients in the unadjusted analysis was 663 (the NH group was excluded in this analysis) except when estimating prostate cancer prevalence where the total number of patients was 521.

There is a trend of increasing prevalence of BC with age and smoking mainly in the VH group. There seems to be a similar trend in the NVH group, but due to the limited number of patients, there are age ranges with few or no cancer diagnoses. Thus, in the VH group, with the exception of 1 case of BC in a patient aged <35 years, the remaining cases of cancer occurred in patients over 45 years of age. Regarding the NVH group, no cancer was diagnosed in patients aged <45 years and only one case of upper urinary tract and renal cancer was observed in patients aged over 70 years.

As for smoking, in patients with VH an overall prevalence of cancer was observed in never smokers of 19.7%, 25.2% in current smokers and 44.9% in ex-smokers. In the NVH group, the prevalence was 20% in never smokers, 33.3% in ex-smokers and 40% in smokers.

Table 3 shows the adjusted and unadjusted cancer prevalence estimates according to type of hematuria and cancer. Regardless of the type of hematuria, the unadjusted BC prevalence was 34.8% (95% CI 31.21—38.47) while the adjusted prevalence was 30.2% (95% CI 23.18—38.23). In all the calculations performed, the unadjusted prevalence was higher than the adjusted prevalence.

Finally, Table 4 presents the association between risk factors and the prevalence of the different types of cancer. It shows that age (OR1.04 (95% CI 1.03—1.06; $P < 0.001$)), presence of VH (OR 2.25 (95% CI 1.13—4.48; $P = 0.021$)) and smoking (ex-smokers: OR 2.27 (95% CI 1.39—3.69; $P = 0.002$); smokers: OR 2.58 (95%CI 1.52—4.35; $P = 0.001$)) are associated with increased odds of bladder cancer.

## Discussion

This analysis presents the prevalence of cancer in a cohort of patients referred to the urology service with suspected urinary tract cancer, mainly due to hematuria. Specifically, the data analyzed were obtained from the patients of the Spanish cohort of the IDENTIFY study.

BC presented the highest prevalence compared to the other cancers analyzed, accounting for around 1% of all cancers (10 UTUC, 9 renal cancer and 5 prostate cancer). These results were expected due to the lower prevalence of TUS and renal cancer. A low prostate cancer prevalence is observed since this is a cohort of patients referred mainly for hematuria, which is not a common form of prostate cancer presentation.

Other studies report BC prevalence rates of 8—11.9%[18—21] in patients referred for hematuria, while our analysis showed an overall prevalence of 36.7%.

Specifically, the IDENTIFY study found an adjusted prevalence of cancer of 28.2% (22.3—34.1)[14] while in this study it was 32.7% (24.90—41.54). This difference may be due to the percentage of patients referred with VH and NVH. In our analysis, 83.7% of patients had VH compared to 65.4% of the international cohort.[14] We also observed differences with respect to smoking. In our series, the percentage of patients who were smokers/ex-smokers was 62.5% compared to 48% in the international cohort.[14] These differences may justify the higher prevalence of cancer. They also reinforce the association between macroscopic hematuria and smoking with the probability of cancer diagnosis and the need to complete the diagnostic evaluation in this type of patient. It should be noted that the adjusted prevalence of cancer found, as in the IDENTIFY study, is mainly attributable to BC, due to the low prevalence of the remaining cancers.

The authors of the IDENTIFY study highlight that country-specific BC prevalence varied greatly, which is the most important factor in determining the adjusted prevalence.[14] In the international series, the unadjusted prevalence of BC was 17.1% and the adjusted prevalence was 24.7%. In the Spanish cohort, the crude prevalence of BC was 36.7% and adjusted prevalence was 30.2%. Adjustment for center of origin highlights the difference in prevalence between hospitals. It is likely that centers with a greater volume of patients showed higher cancer prevalence rates. This reinforces the

**Table 4** Association of risk markers with prevalence of urinary tract cancers.

| | All cancers (249/663) | | Bladder cancer (231/663) | | UTUC (10/663) | | Renal cancer (9/663) | | Prostate cancer (4/521) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | OR (95% CI) | P | OR (95% CI) | P | OR (95% CI) | P | OR (95% CI) | P | OR (95% CI) | P |
| Age | 1.05 (1.03—1.06) | <0.001 | 1.04 (1.03—1.06) | <0.001 | 1.04 (0.98—1.11) | 0.21 | 1.01 (0.96—1.07) | 0.66 | 1 (0.92—1.07) | 0.91 |
| **Hematuria** | | | | | | | | | | |
| NVH | 1 | | 1 | | 1 | | 1 | | 1 | |
| VH | 2.19 (1.13—4.24) | 0.02 | 2.25 (1.13—4.48) | 0.02 | 1.04 (0.11—9.53) | 0.98 | 1.04 (0.11—9.41) | 0.97 | 2346655 (0 - NA) | 0.99 |
| **Sex** | | | | | | | | | | |
| Female | 1 | | 1 | | 1 | | 1 | | – | |
| Male | 0.95 (0.60—1.52) | 0.84 | 1.01 (0.63—1.62) | 0.98 | 0.36 (0.07—1.79) | 0.21 | 0.80 (0.18—3.51) | 0.77 | – | |
| **Smoking** | | | | | | | | | | |
| Never smoked | 1 | | 1 | | 1 | | 1 | | | |
| Ex-smoker | 2.11 (1.30—3.40) | 0 | 2.27 (1.39—3.69) | 0 | 2.97 (0.47—18.86) | 0.25 | 0.16 (0.02—1.44) | 0.1 | 0.42 (0.06—3.14) | 0.4 |
| Current smoker | 2.36 (1.40—3.95) | 0 | 2.58 (1.52—4.35) | <0.001 | 1.64 (0.21—12.92) | 0.64 | 0.23 (0.03—2.05) | 0.19 | 6.89e-08 (0 - NA) | 0.99 |
| **Random effects variance** | | | | | | | | | | |
| Center | 0.51 (0.30—0.89) | | 0.47 (0.27—0.83) | | 0.73 (7.19e-06—0.96) | | 6.51e-11 (0 - NA) | | 2.32 (0.50—10.72) | |

importance of multicenter data collection, improving quality and decreasing selection bias associated with patient inclusion. Of the nine centers included in the Spanish cohort, five of them are third-level centers.

Patients referred with NH were included in the study to minimize selection bias and reflect clinical practice. As in the IDENTIFY study, many of these patients had been referred with suspected malignancy, mainly after imaging tests. This justifies the high proportion of patients with a diagnosis of cancer. We observed that out of 43 patients, 28 had BC. This rate is higher than that of the IDENTIFY study, in which 203 of the 614 patients referred without hematuria(NH) had cancer.

Consistent with the IDENTIFY study, the prevalence of cancer increased with age. In the VH group, one patient aged <35 years had BC detected, which reinforces the importance of performing a complete diagnostic study in patients presenting with this clinical picture. With respect to the NVH group, no cases of cancer were observed in patients aged <45 years and only 2 in the international cohort.

Multivariable analysis showed that age, smoking and VH were significantly associated with all cancers, especially due to BC. This further supports the association between smoking and hematuria with BC. These conclusions cannot be extended to other types of cancer due to their low prevalence. Wider caseloads of these cancers would be recommended to assess whether the association seen with BC is valid for UTUC and renal cancers.

Overall, the trends observed in the results of the IDENTIFY study are similar to those obtained from the analysis of the Spanish cohort. The higher prevalence of cancer observed in our series, mainly bladder cancer, is at the expense of a higher rate of patients with VH and smok-

ing. Therefore, future recommendations presented by the IDENTIFY working group should be adopted in the strictest manner due to the possibility of a higher incidence of cancer in our cohort of patients.

One limitation of the present work is generalizability to the general population. The study focuses on a subgroup of patients referred for suspected urinary tract cancer, especially with hematuria and does not evaluate all those patients initially triaged at a primary care level.

## Conclusion

This study highlights the risk of BC in patients with VH and smoking habits. BC presented the highest prevalence, even higher than that reported in previous series and presented in the IDENTIFY study. Future work should evaluate other associated factors that allow us to create cancer prediction models to further increase cancer detection in our patients.

## Conflicts of interest

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

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## Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acuroe.2023.08.001.

## 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. International Journal of Cancer. Wiley-Liss Inc. 2019;144:1941–53.
2. Miyazaki J, Nishiyama H. Epidemiology of urothelial carcinoma. Int J Urol. 2017;24:730–4, http://dx.doi.org/10.1111/iju.13376.
3. Dy GW, Gore JL, Forouzanfar MH, Naghavi M, Fitzmaurice C. Global Burden of Urologic Cancers, 1990–2013. European Urology. Elsevier B.V. 2017;71:437–46.
4. Yaxley J. Urinary tract cancers: An overview for general practice. J Family Med Prim Care. 2016;5:533.
5. DeGeorge KC, Holt HR, Hodges SC. Bladder Cancer: Diagnosis and Treatment. Am Fam Physician. 2017;96:507–14.
6. Bolenz C, Schröppel B, Eisenhardt A, Schmitz-Dräger BJ, Grimm MO. The Investigation of Hematuria. Dtsch Arztebl Int. 2018;115:801–7, http://dx.doi.org/10.3238/arztebl.2018.0801.
7. Peterson LM, Reed HS. Hematuria. Prim Care. 2019;46:265–73, http://dx.doi.org/10.1016/j.pop.2019.02.008.
8. Barocas D, Boorjian S, Alveraz J, et al, Accessed: 20 June 2022. Available from: https://www.auanet.org/guidelines/microhematuria, 2020.
9. Price SJ, Shephard EA, Stapley SA, Barraclough K, Hamilton WT. Non-visible versus visible haematuria and bladder cancer risk: A study of electronic records in primary care. Br J Gen Pract. 2014;64:e584–9.
10. 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. 2018;8:1129.
11. 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;97:301–5.
12. 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;21:8–12.
13. 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;126:34–8.
14. Khadhouri S, Gallagher KM, MacKenzie KR, Shah TT, Gao C, Moore S, et al. The IDENTIFY study: The investigation and detection of urological neoplasia in patients referred with suspected urinary tract cancer – A multicentre observational study. BJU Int. 2021;128:440–50.
15. Khadhouri S, Gallagher KM, MacKenzie KR, Shah TT, Gao C, Moore S, et al. Developing a Diagnostic Multivariable Prediction Model for Urinary Tract Cancer in Patients Referred with Haematuria: Results from the IDENTIFY Collaborative Study. Eur Urol Focus. 2022;8:1673–82.
16. Gelband, Hellen; Jha, Prabhat; Sankaranarayanan, Rengaswamy; Horton, Susan. 2015. Disease Control Priorities, Third Edition: Volume 3. Cancer. Washington, DC: World Bank. © World Bank. Accessed: 20 jun 2022. Available at: https://openknowledge.worldbank.org/handle/10986/22552 License: CC BY 3.0 IGO.
17. Davis R, Jones JS, Barocas DA, Castle EP, Lang EK, Leveillee RJ, et al. American Urological Association. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. J Urol. 2012;188 Suppl 6:2473–81, http://dx.doi.org/10.1016/j.juro.2012.09.078.
18. 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. Eur Urol. 2018;74:10–4.
19. 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;97:301–5.
20. 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;163:524–7.
21. Gaya JM, Territo A, Woldu S, Schwartzmann I, Verri P, González-Pérez L, et al. Incidental diagnosis of bladder cancer in a national observational study in spain. Actas Urol Esp (Engl Ed). 2022. S2173-5786(22)00104-4.