Prevalence of urinary tract cancer in the Spanish cohort of the IDENTIFY studyPrevalencia del cáncer del tracto urinario. Análisis de la cohorte española del estudio IDENTIFY

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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 IDENTIFY 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.

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.

Keywords
HematuriaUrinary tract cancerUrothelial carcinomaBladder cancerRenal cancerRisk factors
Palabras clave
HematuriaCáncer del tracto urinarioCarcinoma urotelialCáncer vesicalCáncer renalFactores de riesgo

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, 12, 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 cancer 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 cancer 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 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 diagnosed 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.

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], [19], [20], [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 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 smoking. 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.

Author contributions

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.