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Cancer Prevalence and Risk Stratification in Adults Presenting With Hematuria: A Population-Based Cohort Study

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Abstract

Objective: To calculate the prevalence of renal cell carcinoma (RCC), upper urinary tract urothelial carcinoma (UT-UC), and lower urinary tract urothelial carcinoma (LT-UC) in patients with gross asymptomatic microhematuria (AMH) and symptomatic microhematuria (SMH).

Patients and Methods: This study was a population-based retrospective descriptive study. The study was approved by both the Mayo Clinic Institutional Review Board and the Olmsted Medical Center Institutional Review Board, and the population used was Olmsted County residents. A total of 4453 patients who presented with an initial episode of hematuria from January 1, 2000, through December 30, 2010, were included. Of the 4453 patients (median age, 58 years; interquartile range, 44.6-73.3 years), 1487 (33.4%) had gross hematuria, 2305 (51.8%) had AMH, and 661 (14.8%) had SMH.

Results: In the 1487 patients with gross hematuria, the prevalence of RCC, UT-UC, and LT-UC was 1.3%, 0.8%, and 9.0%, respectively. In the 2305 patients with AMH, the prevalence of RCC, UT-UC, and LT-UC was 0.2%, 0.3%, and 1.6%, respectively. In the 661 patients with SMH, the prevalence of RCC, UT-UC, and LT-UC was 0.6%, 0.2%, and 0.3%, respectively. Age was the most relevant risk factor for any hematuria type.

Conclusion: This unique cohort study reported that the prevalence of RCC or UC in patients with AMH and SMH was low, especially in the young cohort, and a large number of intense work-ups, such as cystoscopy and computed tomography urography, currently conducted could be omitted if stratified by hematuria type and age.

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Hematuria is one of the most common urinary findings that motivate patients to seek medical attention, particularly when they present with gross hematuria (GH). According to data from medical checkups, the prevalence of asymptomatic microhematuria (AMH) is between 5% and 20%.[1-3] Patients with AMH are typically examined for the presence or absence of medical renal diseases such as nephropathy and nephritis through initial inspections, including urine tests and blood tests.[4] When no renal parenchymal disease is identified, patients are examined for malignant tumors in the kidney and urinary tract.

The standard methodology for lower urinary tract urothelial cancer (LT-UC) detection is cystoscopy; imaging such as ultrasonography and computed tomography (CT) urography is limited in the identification of small bladder urothelial cancer (UC). Computed tomography with and without enhancement in the nephrographic phase is the best modality to detect renal cell carcinoma (RCC), but the excretory phase is unnecessary. Computed tomography urography including an excretory phase has the highest sensitivity for the identification of upper urinary tract UC (UT-UC), but its disadvantage is radiation exposure and long examination time.[5] Although the sensitivity of ultrasonography for

RCC and UC and urinary stones is lower than that of CT urography, it has the advantage of being noninvasive and low cost.[6]

The scope of application and the choice of these detailed examinations vary depending on the guidelines.[4,7-13] The American Urological Association (AUA) guidelines on microhematuria has the widest scope of application for detailed examinations and recommends cystoscopy and CT urography for patients at risk of malignant tumors, such as those aged 35 years and older, men, and smokers.[4] Although accurate detection of malignant tumors is desired for the work-up of patients with hematuria, an optimal examination corresponding to the risk of malignant tumor should be chosen not to expose patients without malignancy to unnecessary hazards.

To estimate the cancer risk in patients with hematuria, it is necessary to determine the accurate cancer prevalence rates. The prevalence rates and risk factors for malignant tumors in patients with hematuria have been reported from single- and multicenter research studies.[6,14-24] However, this research reports an apparent increase in prevalence because of referral bias, and the diagnostic guidelines for patients with hematuria subject even low-risk patients to detailed examinations. There have been reports suggesting that this issue has led to a decrease in the adherence rate with AUA guidelines in actual clinical practice.[25] A practical risk stratification has been desired to optimize the balance of advantages, harms, and costs.[26,27] Herein, we carried out a population-based epidemiological study to calculate the accurate prevalence of malignant tumors in the kidney and urinary tracts in adult patients with hematuria and to develop risk stratification.

PATIENTS AND METHODS

This study is a retrospective population-based epidemiological analysis. The protocol for this study was approved by the Mayo Clinic Institutional Review Board and the Olmsted Medical Center Institutional Review Board.

Inclusion/Exclusion Criteria for Participants

The population for this study was derived from Olmsted County, Minnesota, patients followed by the Rochester Epidemiology Project (REP). The REP is a compilation of medical records of all health care organizations in Olmsted County, enabling the longitudinal analysis of a local patient's complete medical history.[28-30] All patient data were retrieved from the archived medical records of Mayo Clinic in Rochester, Minnesota; Olmsted Medical Center; and the Rochester Family Medicine Clinic. These institutions provide 90% to 96% of health care for Olmsted County residents.[31]

The study population was derived from Olmsted County residents who presented with hematuria from January 1, 2000, through December 30, 2010. Patients were excluded on the basis of the following criteria: mortality from other than RCC and UC in the 3-year observation period, age less than 18 years, pregnancy at the time of presentation, documentation of previous malignant tumors in the kidney or urinary tract, diagnosis of medical renal disease or prostate cancer, questionable hematuria diagnosis, red blood cell (RBC) count less than 3 cells per high power visual field (according to the definition of AUA hematuria guidelines).[4] Patients were excluded if hematuria was a result of trauma or catheter placement. Supplemental Figure (available online at http://www.mcpiqojournal.org) depicts a flowchart based on exclusion and inclusion criteria for subjects.

Data Retrieval

Using the REP database, we initially identified 11,917 adult patients who were diagnosed with hematuria in the study timeframe by using *International Classification of Diseases, Ninth Revision* diagnosis codes (599.7x). We classified each hematuria episode as GH (599.71), microhematuria (599.72), or hematuria and unspecified (599.70), and then performed a manual chart review for confirmation and for properly classifying patients with unspecified hematuria. Microhematuria with associated pain, bladder irritation, dysuria, and urinary frequency at the time of its discovery was categorized as symptomatic microhematuria (SMH). We used the REP database to retrieve medical information, including date of diagnosis, patient age at the onset of hematuria, sex, race, smoking history, date of diagnosis of hematuria, and presence or absence of renal disease, urinary tract infection (UTI), urolithiasis, and renal and urinary tract malignant tumors that could cause hematuria, such as RCC and UC.

TABLE 1. Characteristics of Adult Patients With Hematuria and Types of Hematuria, Including Gross Hematuria, Symptomatic Microscopic Hematuria, and Asymptomatic Microscopic Hematuria in a Population-Based Cohort From 2000 to 2010[a,b]

Characteristic	Total patients with hematuria	Types of hematuria		
		Gross hematuria	Symptomatic microscopic hematuria	Asymptomatic microscopic hematuria
Total number	4453	1487 (33.4%)	661 (14.8%)	2305 (51.8%)
Demographic characteristics				
Sex				
Male	2150 (48.3)	838 (56.4)	287 (43.4)	1025 (44.5)
Female	2303 (51.7)	649 (43.6)	374 (56.6)	1280 (55.5)
χ^2 test	P=.218	P<.001	P<.001	P<.001
Age				
Overall	58 (44-73)	58 (43-74)	49 (35-62)	60 (47-74)
Male	60 (46-74)	60 (44-76)	52 (37-65)	62 (4-75)
Female	56 (43-72)	56 (41-70)	48 (35-61)	60 (47-74)
t test	P<.001	P<.001	P=0.016	P=0.030
Race/ethnicity				
White	3943 (89)	1343 (90)	553 (84)	2047 (89)
Black	142 (3.2)	29 (2.0)	40 (6.1)	73 (3.2)
Hispanic	121 (2.7)	46 (3.1)	25 (3.8)	50 (2.2)
Asian	150 (3.4)	36 (2.4)	31 (4.7)	83 (3.6)
Other	63 (1.4)	23 (1.5)	10 (1.5)	30 (1.3)
Unknown	34 (0.8)	10 (0.7)	2 (0.3)	22 (1.0)
χ^2 test	P<.001	P<.001	P<.001	P<.001
Tobacco use				
Total	1669 (37)	584 (39)	248 (38)	837 (36)
Male	920 (21)	376 (25)	109 (16)	435 (19)
Female	749 (17)	208 (14)	139 (21)	402 (17)
Fisher exact test	P<.001	P<.001	P=.871	P<.001
Previous hematuria history (+)				
Total	599 (13)	189 (13)	67 (10)	343 (15)
Male	307 (6.9)	122 (8.2)	24 (3.6)	161 (7.0)
Female	292 (6.6)	67 (4.5)	43 (6.5)	182 (7.9)
Fisher exact test	P=.124	P=.015	P=.196	P=.346
Maximum urine red blood cell count				
3-10	1737 (39.0)	226 (15.2)	261 (39.5)	1250 (54.2)
11-20	495 (11.1)	129 (8.7)	91 (13.8)	275 (11.9)
21-50	458 (10.2)	153 (10.3)	79 (11.9)	226 (9.8)
51-100	338 (7.5)	140 (9.4)	55 (8.3)	143 (6.2)
>100	1425 (32.0)	839 (56.4)	175 (26.4)	411 (17.8)
χ^2 test	P<.001	P<.001	P<.001	P<.001

+ = positive.

[a]Data are presented as median (interquartile range) or as No. (percentage).

[b]Noncolored cells indicate no statistical significance ($P \geq .05$), whereas light-gray colored cells indicate statistical significance ($P < .05$).

Diagnosis of the Cause of Hematuria

Information on the type of cancer (RCC, UC of the renal pelvis, ureter, bladder, and urethra) and the date of diagnosis were obtained from the REP database, Mayo Clinic tumor registry, and medical chart review. Renal pelvis cancer and ureteral cancer were classified as UT-UC, whereas bladder cancer and

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urethral cancer were classified as LT-UC. To minimize false-negative cases of malignancy, a 3-year follow-up period was set. Urolithiasis was confirmed for subjects if it had been reported via a diagnostic imaging report. Urinary tract infection was confirmed for subjects if it had been assigned an *International Classification of Diseases, Ninth Revision* code (595: cystitis or 590: infection of kidney) within 1 month of hematuria diagnosis.

Statistical Analyses

JMP 11.0.0 (SAS Institute) was used as the statistical analysis software.

The age at onset of hematuria was categorized into groups of 18 to 34, 35 to 44, 45 to 54, 55 to 64, 65 to 74, and 75 years and older. The maximum urinary RBC count per high power field was categorized into groups of 3 to 10, 11 to 20, 21 to 50, 51 to 100, and 101 and more RBCs per high power field.

We performed univariate analysis to detect the difference in patient risk factors between patients with cancer and patients without cancer for all patients with hematuria and, separately, for the GH, AMH, and SMH groups. Pearson's chi-square test was used for categorical variables and the Fisher exact test was used for binary variables for comparative tests between malignant tumor—afflicted and nonafflicted groups. To stratify the risk of malignant tumors, multivariable logistic regression analysis was conducted for each of the GH group, AMH group, and SMH group. All variables that were evaluated in the univariate analysis were used for the first analysis regardless of the significant difference in univariate analysis, and then only the variables that make the multivariable logistic regression analysis calculation unstable were eliminated from the final model. A 2-tailed *P* value of less than .05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 4453 patients met all inclusion criteria (see the Supplemental Figure). Of these, 1487 were patients with GH, 2305 were patients with AMH, and 661 were patients with SMH. The patient characteristics included a median age of 58 years (interquartile range, 44-73 years) (Table 1). Patients

TABLE 2. Prevalence of Disease in Patients With Hematuria Overall, Stratified by Sex Subgroups, and the Percentage of Diagnoses Presenting as Types of Hematuria, Including Gross, Symptomatic Microscopic, and Asymptomatic Microscopic Hematuria[a,b]

Variable	Unknown etiology[c]	Cancer	RCC	UT-UC			LT-UC			Stone	UTI	Total
				Renal pelvis UC	Ureter UC		Bladder UC	Urethra UC				
Hematuria overall	2761 (62)	210 (4.7)	28 (0.6)	20 (0.5)[d]	12 (0.3)[d]	11 (0.2)[d]	172 (3.9)	170 (3.8)	2 (0)	608 (14)	1034 (23)	4453
Sex												
Male	1363 (62)	146 (6.8)	15 (0.7)	12 (0.6)[d]	6 (0.3)[d]	7 (0.3)[d]	125 (5.8)	124 (5.8)	1 (0)	374 (17)	352 (16)	2150
Female	1410 (61)	64 (2.8)	13 (0.6)	8 (0.4)[d]	6 (0.3)[d]	4 (0.2)[d]	47 (2.0)	46 (2.0)	1 (0)	234 (10)	682 (30)	2303
Hematuria types												
Gross	682 (46)	158 (10.6)	20 (1.3)	12 (0.8)[d]	8 (0.5)[d]	6 (0.4)[d]	134 (9.0)	132 (8.9)	2 (0.1)	263 (18)	472 (32)	1487
Symptomatic microscopic	366 (55)	7 (1.1)	4 (0.6)	1 (0.2)	1 (0.2)	1 (0.2)	2 (0.3)	2 (0.3)	0 (0)	192 (29)	130 (20)	661
Asymptomatic microscopic	1713 (74)	45 (2.0)	4 (0.2)	7 (0.3)	3 (0.1)	4 (0.2)	36 (1.6)	36 (1.6)	0 (0)	153 (6.6)	432 (19)	2305

[a]LT-UC = lower tract urothelial carcinoma; RCC = renal cell carcinoma; UC = urothelial carcinoma; UTI = urinary tract infection; UT-UC = upper tract urothelial carcinoma.
[b]Data are presented as No. (percent prevalence).
[c]Defined as no cancer, stone, or UTI diagnosed.
[d]Subgroup cancers may not add up to upper tract or lower tract numbers because of patients with multiple synchronous urothelial carcinoma diagnoses (ie, both renal pelvis and ureter in 3 patients with gross hematuria: 1 male and 2 female patients).

TABLE 3. Accumulated Prevalence of RCC and Upper and Lower Urinary Tract UC in Patients With Hematuria Stratified by Age Category and Types of Hematuria[a,b]

			RCC			Upper tract UC			Lower tract UC		
Type of hematuria	Age category (y)	No. of patients with hematuria	No. of patients	Prevalence	Cumulative prevalence	No. of patients	Prevalence	Cumulative prevalence	No. of patients	Prevalence	Cumulative prevalence
Asymptomatic microhematuria											
	18-34	176	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0
	35-44	276	0	0.0	0.0	0	0.0	0.0	1	0.4	0.4
	45-54	422	1	0.2	0.2	0	0.0	0.0	1	0.2	0.6
	55-64	435	0	0.0	0.2	3	0.7	0.7	12	2.8	3.4
	65-74	419	2	0.5	0.7	1	0.2	0.9	5	1.2	4.6
	≥75	573	1	0.2	0.9	3	0.5	1.5	17	3.0	7.5
Symptomatic microhematuria											
	18-34	144	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0
	35-44	122	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0
	45-54	126	1	0.8	0.8	0	0.0	0.0	0	0.0	0.0
	55-64	115	2	1.7	2.5	0	0.0	0.0	0	0.0	0.0
	65-74	73	0	0.0	2.5	0	0.0	0.0	1	1.4	1.4
	≥75	80	1	1.3	3.8	1	1.3	1.3	1	1.3	2.6
Gross hematuria											
	18-34	203	1	0.5	0.5	0	0.0	0.0	1	0.5	0.5
	35-44	182	1	0.5	1.0	0	0.0	0.0	1	0.5	1.0
	45-54	260	6	2.3	3.3	0	0.0	0.0	12	4.6	5.7
	55-64	253	2	0.8	4.1	1	0.4	0.4	24	9.5	15.1
	65-74	224	5	2.2	6.4	2	0.9	1.3	23	10.3	25.4
	≥75	365	5	1.4	7.7	9	2.5	3.8	73	20.0	45.4

[a]RCC = renal cell carcinoma; UC = urothelial carcinoma.
[b]Accumulated prevalence > 1% is shaded.

TABLE 4. Univariate Analysis of Risk Factors for RCC and UC in Patients With Hematuria Stratified by Types of Hematuria[a,b,c,d]

Hematuria type	Variable (reference)	RCC and any UC	RCC	UT-UC	LT-UC
Gross hematuria	Age	<.001 1.05	.350 1.01	<001 1.07	<.001 1.05
	History of smoking (no smoking)	<.001 2.51 (1.80-3.52)	.648 1.27 (0.52-3.08)	.774 0.77 (0.23-2.57)	<.001 2.67 (1.86-3.85)
	History of hematuria (no hematuria history)	.163 1.40 (0.90-2.21)	.733 1.21 (0.35-4.19)	.188 2.33 (0.62-8.67)	.175 1.39 (0.86-2.27)
	Sex (female)	<.001 2.02 (1.41-2.90)	.895 0.63 (0.26-1.53)	.249 2.3 (0.63-8.67)	<.001 2.26 (1.51-3.35)
	Race	.052	.898	.935	.066
	RBC count	<.001 1.29	.08 1.42	.20 1.38	.002 1.25
Asymptomatic microscopic hematuria	Age	<.001 1.04	.578 1.02	.09 1.04	<.001 1.04
	History of smoking (no smoking)	.004 2.44 (1.34-4.44)	.139 5.28 (0.54-50.8)	.107 4.41 (0.85-22.8)	.053 1.98 (1.02-3.84)
	History of hematuria (no hematuria history)	.394 0.55 (0.20-1.55)	.107 5.75 (0.81-40.9)	.999 0.95 (0.11-7.94)	.154 0.33 (0.08-1.39)
	Sex (female)	.022 2.09 (1.14-3.83)	.999 1.25 (0.18-8.88)	.999 0.94 (0.21-4.19)	.004 2.88 (1.41-5.89)
	Race	.755	.992	.971	.871
	RBC count	.09 1.16	.389 .66	.133 1.39	.105 1.18
Symptomatic microscopic hematuria	Age	.006 1.06	.16 1.04	.08 1.19	.08 1.08
	History of smoking (no smoking)	.717 0.66 (0.13-3.45)	.303 0.18 (0.01-3.42)	.999 0.55 (0.02-13.66)[e]	.140 8.39 (0.40-175.43)[e]
	History of hematuria (no hematuria history)	.999 0.58 (0.03-10.27)[e]	.999 0.97 (0.06-18.25)[e]	.999 0.04 (0.00-0.94)[e]	.999 1.76 (0.08-36.95)[e]
	Sex (female)	.047 7.96 (0.95-66.5)	.035 11.9 (0.64-221.73)[e]	.999 0.43 (0.02-10.67)[e]	.188 6.56 (0.34-137.16)[e]
	Race	.818	.978	.001	.996
	RBC count	.345 1.24	.705 1.12	.850 1.12	.309 1.65

[a]LT-UC = lower tract urothelial carcinoma; RBC = red blood cell; RCC = renal cell carcinoma; UC = urothelial carcinoma; UT-UC = upper tract urothelial carcinoma.
[b]Upper and lower rows in cells of continuous variables are P values and odds ratios associated with 1-nit increase, respectively.
[c]Upper and lower rows in cells of binary variables are *P* values and odds ratios (95% CIs), respectively.
[d]Noncolored cells indicate no statistical significance ($P \geq .05$), whereas light-gray colored cells indicate statistical significance ($P < .05$).
[e]Haldane-Anscombe correction was used for the estimation of odds ratios with zeros.

presenting with symptomatic microscopic hematuria were younger than patients presenting with GH or AMH (median age, 52 years vs 60 and 61 years). Approximately half of the patients were female (n=2303 [52%]), and one-third had a history of smoking (n=1669 [37%]). This distribution was similar between the 3 hematuria groups. Patients underwent 6 procedures for the hematuria work-up: cystoscopy, abdominal ultrasonography, intravenous urography, unenhanced CT, enhanced CT without excretory phase, and CT urography. The number of patients for each procedure was as follows: patients with GH (n=1487), 627 (42%), 223 (15%), 270 (18%), 168 (11%), 107 (7%), and 367 (25%), respectively; patients with AMH (n=2305), 697 (30%), 475 (21%), 290

TABLE 5. Multivariable Logistic Regression Analysis of Risk Factors for RCC and UC in Patients With Hematuria Stratified by Types of Hematuria[a,b,c,d,e]

Hematuria type	Variable (reference)	RCC and any UC	RCC	UT-UC	LT-UC
Gross hematuria	Age	<.001 1.04 (1.03-1.06)	.511 1.00 (0.98-1.03)	.004 1.06 (1.02-1.12)	<.001 1.05 (1.03-1.06)
	History of smoking (no smoking)	<.001 2.43 (1.70-3.48)	.556 1.31 (0.52-3.23)	.563 0.69 (0.18-2.30)	<.001 2.58 (1.76-3.82)
	History of hematuria (no hematuria history)	.862 0.96 (0.58-1.52)	.829 1.15 (0.26-3.52)	.531 1.53 (0.33-5.38)	.730 0.91 (0.53-1.50)
	Sex (female)	.019 1.56 (1.08-2.30)	.213 0.56 (0.22-1.39)	.287 2.07 (0.59-9.65)	.011 1.72 (1.14-2.64)
	RBC count	.024 1.17 (1.34-0.86)	.101 3.81 (0.92-24.9)	.529 1.17 (0.75-2.16)	.148 1.10 (0.96-1.28)
Asymptomatic microscopic hematuria	Age	<.001 1.03 (1.02-1.06)	.459 .63 (.14-1.35)	.108 1.04 (0.99-1.10)	<.001 1.04 (1.02-1.06)
	History of smoking (no smoking)	.003 2.48 (1.35-4.65)	.141 5.60 (0.69-115.23)	.048 5.41 (1.12-38.8)	.062 1.91 (0.96-3.79)
	History of hematuria (no hematuria history)	.173 0.51 (0.15-1.29)	.094 5.38 (0.64-45.2)	.993 0.99 (0.05-5.92)	.101 0.30 (0.04-1.00)
	Sex (female)	.064 1.78 (0.96-3.38)	.948 1.07 (0.13-9.09)	.588 0.65 (0.13-3.06)	.010 2.60 (1.29-5.59)
	RBC count	.494 1.06 (0.88-1.27)	.355 0.16 (0.00-3.30)	.244 2.88 (0.47-18.7)	.542 1.06 (0.97-3.79)
Symptomatic microscopic hematuria	Age	.004 1.07 (1.02-1.12)	.16 1.04 (0.98-1.10)	.001 1.20 (1.03-1.64)	.07 1.07 (0.99-1.19)
	History of smoking (no smoking)	.429 0.52 (0.07-2.52)	—	—	—
	History of hematuria (no hematuria history)	—	—	—	—
	Sex (female)	.023 7.91 (1.29-152.78)	—	—	—
	RBC count	.711 1.09 (0.68-1.79)	.080 1.08 (0.57-2.00)	.742 0.82 (0.18-3.57)	.370 1.51 (0.62-6.21)

[a]LT-UC = lower tract urothelial carcinoma; RBC = red blood cell; RCC = renal cell carcinoma; UC = urothelial carcinoma; UT-UC = upper tract urothelial carcinoma.
[b]Upper and lower rows in cells of continuous variables are P values and odds ratios associated with 1-nit increase, respectively.
[c]Upper and lower rows in cells of binary variables are *P* values and odds ratios (95% CIs), respectively.
[d]Dash indicates that the parameter was not used for multivariable analysis.
[e]Noncolored cells indicate no statistical significance ($P \geq .05$), whereas light-gray colored cells indicate statistical significance ($P < .05$).

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(13%), 77 (3%), 88 (4%), and 365 (16%), respectively; patients with SMH (n=664), 128 (19%), 116 (18%), 86 (13%), 197 (30%), 152 (23%), and 84 (13%), respectively.

Prevalence of Diseases

The prevalence data of RCC, UC, urolithiasis, and UTIs in the study cohort are presented in Table 2. Of the 4453 patients with hematuria, RCC and UC were observed in 210 subjects (4.7%). A total of 28 subjects were diagnosed with RCC (0.6%), 12 with renal pelvic UC (0.3%), 11 with ureteral UC (0.2%), 170 with bladder UC (3.8%), and 2 with urethral UC (0.04%). Upper urinary tract UC (renal pelvic and ureter UC) was present in 20 subjects (0.5%), whereas LT-UC (bladder and urethral UC) was present in 172 subjects (3.9%). In 2761 of 4453 subjects (62%), the etiology of hematuria was not determined. Eleven of 210 patients with cancer (5.2%) had 2 separate primary malignant neoplasms; 3 patients had RCC and LT-UC, 1 patient had renal pelvic UC and ureter UC, and 7 patients had UT-UC and LT-UC. Of the 170 subjects with bladder UC, 7 (4.1%) had UT-UC, whereas of the 20 subjects with UT-UC, 7 (35%) had bladder UC combined. Of the 210 patients with cancer, 55 (26%) were found to also have urolithiasis or UTI.

The prevalence of malignant tumors was 11% in patients with GH, 1.1% in patients with SMH, and 2.0% in patients with AMH. In the 1487 patients with GH, the prevalence of RCC, UT-UC, and LT-UC were 1.3%, 0.8%, and 9.0%, respectively. In the 661 patients with SMH, the prevalence of RCC, UT-UC, and LT-UC were 0.6%, 0.2%, and 0.3%, respectively. In the 2305 patients with AMH, the prevalence of RCC, UT-UC, and LT-UC were 0.2%, 0.3%, and 1.6%, respectively. The prevalence of stones was 18% in patients with GH, 29% in patients with SMH, and 6.6% in patients with AMH. The prevalence of UTI was 32% in patients with GH, 20% in patients with SMH, and 19% in patients with AMH.

Table 3 presents the results of the prevalence of RCC and UC stratified by age category. The prevalence of RCC and UC was extremely low in patients with AMH and SMH younger than 55 years, whereas the prevalence of RCC and LT-UC exceeded 1% in patients with GH older than 35 years. However, the prevalence of UT-UC was extremely low even in patients with GH younger than 65 years.

Risk Stratification of Hematuria

Table 4 presents the results of the univariate analysis. Advanced age category (unit odds ratio [OR], 1.05; $P<.001$), smoking history (OR, 2.51; 95% CI, 1.80 to 3.52; $P<.001$), male sex (OR, 2.02; 95% CI, 1.41 to 2.90; $P<.001$), and a larger number of urinary RBC (unit OR, 1.29; $P<.001$) had a significantly higher prevalence of RCC and UC in the GH group. For RCC and UC, age category (unit OR, 1.04; $P<.001$), history of smoking (OR, 2.44; 95% CI, 1.34 to 4.44; $P=.004$), and male sex (OR, 2.09; 95% CI, 1.14 to 3.83; $P=.022$) were significant factors in the AMH group. For RCC and UC, age (unit OR, 1.06; $P=.006$) and male sex (OR, 7.96; 95% CI, 0.95 to 66.5; $P=.047$) were significant factors in the SMH group.

In the RCC, there was no significant difference between any of the risk factors for any of the types of hematuria, excluding male predominance in the SMH group (OR, 11.9; 95% CI, 0.64 to 221.73; $P=.035$).

For UT-UC, only age category in the GH group (unit OR, 1.07; $P<.001$) and race in the SMH group ($P=.001$) were significant risk factors. We did not identify any significant risk factor for UT-UC in the AMH group.

For LT-UC, age category (unit OR, 1.05; $P<.001$), smoking history (OR, 2.67; 95% CI, 1.86 to 3.85; $P<.001$), male sex (OR, 2.26; 95% CI, 1.51 to 3.35; $P<.001$), and urinary RBC count (unit OR, 1.05; $P=.002$) were risk factors in the GH group. In the AMH group, age category (unit OR, 1.04; $P<.001$) and male sex (OR, 2.88; 95% CI, 1.41 to 5.89; $P=.004$) were significant risk factors. For LT-UC, no significant risk factor was identified in the SMH group.

Table 5 presents the results of the multivariable logistic regression analysis. For RCC, we did not identify any predictive factors for any hematuria type. For UT-UC, only age (unit OR, 1.06; 95% CI, 1.02 to 1.12; $P=.004$) in the GH group, only smoking history (OR, 5.41; 95% CI, 1.12 to 38.8; $P=.048$) in the AMH group, and only age (unit OR, 1.20; 95% CI, 1.03 to 1.64;

P=.001) in the SMH group were significant factors. For LT-UC, age (unit OR, 1.05; 95% CI, 1.03 to 1.06; P<.001), smoking history (OR, 2.58; 95% CI, 1.76 to 3.82; P<.001), and male sex (OR, 1.72; 95% CI, 1.14 to 2.64; P=.011) were significant factors in the GH group. In the AMH group, age (unit OR, 1.04; 95% CI, 1.02 to 1.06; P<.001) and male sex (OR, 2.60; 95% CI, 1.29 to 5.59; P=.010) were significant factors. There was no significant risk factor for LT-UC in the SMH group.

DISCUSSION

Prevalence of Diseases Associated With Hematuria

In this study, we conducted a population-based investigation for estimating an accurate prevalence of RCC and UC in patients with hematuria and developed a risk stratification. The prevalence of RCC and UC in patients with GH and patients with microhematuria had been previously reported to range from 10% to 28% and from 2.9% to 8.9%, respectively.[14-23] However, these were single- or multicenter studies likely affected by referral bias. Although Mohr et al[32] and Thompson[33] had previously conducted population-based research on patients with AMH using the random sampling method, our study is the first population-based study that included the entire relevant population over an 11-year period. In this study, which eliminated referral bias, the prevalence of RCC and UC in patients with GH was 11% whereas the prevalence of malignancies in patients with AMH was 2%. These prevalences belonged to the lowest group compared with previously reported literature.[14-23] In this study, the prevalence of RCC and UC in SMH was 1.1%, which was the lowest among all types of hematuria. This is due to the fact that the frequency of urolithiasis in patients with SMH was highest among all hematuria types, at 29%.

Strategy for Hematuria

There is no fixed opinion on how high the positive predictive value for cancer should be in order for patients to be subjected to detailed examinations during their work-up. In this study, we used a cutoff value of 1% on the basis of the previous literature.[34] According to the results of this study, age and type of hematuria were common risk factors for malignant tumors.

In patients with AMH, the cumulative prevalence of RCC did not exceed 1% even if all aged patients were included. Therefore, intense examination, such as enhanced CT, should not be performed to only detect RCC for patients with AMH. The AUA and Canadian AMH guidelines recommend that cystoscopy and CT urography should be performed on all patients older than 35 and 40 years, respectively, or those with a risk factor for bladder UC.[4,9,35] The prevalence of UT-UC was more than 1% in patients with AMH older than 75 years. Based on this result, it is inefficient to perform CT urography on patients with AMH younger than 75 years, with suspected UT-UC at the initial presentation. This result was consistent with previous reports, suggesting ineffectiveness of CT urography for patients with AMH younger than 50 years.[36-38] Also, Tan et al[6] concluded that CT urography could be safely replaced by ultrasonography because the risk of UT-UC in patients with AMH was extremely low. It is also questionable to perform cystoscopy on all patients stratified by AUA guidelines because the prevalence of LT-UC was only 0.6% in patients younger than 55 years. Indeed, recently, other guidelines recommend a passive work-up for microscopic hematuria for younger ages without symptom.[9,10] Moreover, Swedish guidelines abandon testing for microscopic hematuria.[7] Even if the patient's age is below 55 years, cystoscopy may be adaptable for male patients, which was a significant predictor of LT-UC in our multivariable logistic regression analysis. History of smoking was not a significant predictor of LT-UC in the AMH cohort in this study, in agreement with a previous report,[39] but others reported a significant risk of smoking.[23,40] Patients with risks that were not evaluated in this study, such as occupational exposure of carcinogens or pelvic irradiation, history of genetics, and others, may also be candidates for intense investigation.[4,41]

In patients with GH, the cumulative prevalence of RCC exceeded 1% at the age of 35. The cumulative prevalence of UT-UC in patients younger than 65 years did not exceed 1%, even in patients with GH. Given this

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result, the effectiveness of CT urography, including excretory phase for patients younger than 65 years to identify UT-UC, is questionable even in patients with GH. Noncontrast CT followed by enhanced CT only in the nephrographic phase would be sufficient for patients older than 35 years to detect RCC. It has been reported that the nephrographic phase also has a high sensitivity for identifying UT-UC, which may detect UT-UC in patients who are not examined with CT urography, including an excretory phase.[42] Omission of the excretory phase would contribute to reduced radiation exposure and shortening CT examination time. The prevalence of LT-UC in patients with GH exceeded 1% if the age was greater than 35 years. Cystoscopy is necessary for that cohort.

Bladder irritation is considered to be a risk factor for bladder UC.[4] A Canadian consensus paper on hematuria recommends cystoscopy and CT urography for patients with a single episode of SMH in any age.[35] However, the cumulative prevalence of RCC, UT-UC, and LT-UC was less than 1% in patients younger than 55, 75, and 65 years, respectively, in this study. Hence, intense surveillance such as CT urography and cystoscopy might be omitted for those younger cohorts and ultrasonography or unenhanced CT would be useful to identify stones, UTI, and gross malignant tumors.[13] However, patients with persistent or repeated hematuria should be more thoroughly tested.

Limitations of This Research

Several study limitations exist. First, this was a retrospective study, which may have failed to sufficiently gather information pertaining to risk factors. Second, our patient population was largely white, and future population-based studies should include other races to evaluate risk factors between races. Third, the choice of examination was heterogeneous, depending on the case and physician, and this might affect the sensitivity of disease identification. To reduce false negativity, we set a long follow-up time of 3 years; nevertheless, a small number of malignant tumors might still be missed.[43] Finally, we proposed hematuria type and age cutoff for risk stratification of hematuria, but a further study to develop a specific nomogram using novel risk factors remains necessary.

CONCLUSION

This unique retrospective cohort study reported that the prevalence of RCC or UC in patients with an initial episode of AMH and SMH was low, especially in young cohorts, and a large number of intense work-ups, such as cystoscopy and CT urography in current practice, could be omitted if stratified by hematuria type and age.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AMH** = asymptomatic microhematuria; **AUA** = American Urological Association; **CT** = computed tomography; **GH** = gross hematuria; **LT-UC** = lower urinary tract urothelial carcinoma; **OR** = odds ratio; **RBC** = red blood cell; **RCC** = renal cell carcinoma; **REP** = Rochester Epidemiology Project; **SMH** = symptomatic microhematuria; **UC** = urothelial carcinoma; **UTI** = urinary tract infection; **UT-UC** = upper urinary tract urothelial carcinoma

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