MAYO CLINIC

ORIGINAL ARTICLE

Stratifying Risk of Urinary Tract Malignant Tumors in Patients With Asymptomatic Microscopic Hematuria

Ronald K. Loo, MD; Stephen F. Lieberman, MD; Jeff M. Slezak, MS; Howard M. Landa, MD; Albert J. Mariani, MD; Gary Nicolaisen, MD; Ann M. Aspera, MD; and Steven J. Jacobsen, MD, PhD

Abstract

Objective: To identify patients who could safely avoid unnecessary radiation and instrumentation after the detection of microscopic hematuria.

Patients and Methods: We conducted a prospective cohort study of patients who were referred to urologists and underwent a full evaluation for asymptomatic microscopic hematuria during a 2-year period in an integrated care organization in 3 regions along the West Coast of the United States. A test cohort and validation cohort of patients with hematuria evaluations between January 9, 2009, and August 15, 2011, were identified. Patients were followed passively through their electronic health records for a diagnosis of urothelial or renal cancer. The degree of microscopic hematuria, history of gross hematuria, smoking history, age, race, imaging findings, and cystoscopy findings were evaluated as risk factors for malignant tumors.

Results: The test cohort consisted of 2630 patients, of whom 55 (2.1%) had a neoplasm detected and 50 (1.9%) had a pathologically confirmed urinary tract cancer. Age of 50 years or older and a recent diagnosis of gross hematuria were the strongest predictors of cancer. Male sex was also predictive of cancer, whereas smoking history and 25 or more red blood cells per high-power field on a recent urinalysis were not statistically significant. A Hematuria Risk Index developed from these factors had an area under the receiver operating characteristic curve of 0.809. In the validation cohort of 1784 patients, the Hematuria Risk Index performed comparably (area under the curve = 0.829). Overall, 32% of the population was identified as low risk and 0.2% had a cancer detected; 14% of the population was identified as high risk, of whom 11.1% had a cancer found.

Conclusion: These results suggest that a considerable proportion of patients could avoid extensive evaluations with the use of the Hematuria Risk Index.

© 2013 Mayo Foundation for Medical Education and Research ■ Mayo Clin Proc. 2013;■■(■):1-10

Asymptomatic microscopic hematuria in the general population is common. The prevalence of some degree of hematuria has been reported to be as high as 9% to 18% in large screening studies.[1,2] Even low degrees of microscopic hematuria have been considered a risk factor for urinary tract malignant tumors, and the recommended threshold for evaluation is 3 or more red blood cells per high-power field (RBC/HPF) on 2 of 3 properly performed urinalyses or any high-grade hematuria (>50 RBC/HPF) or gross hematuria.[3] American Urological Association (AUA) best practice policy recommendations include urine testing (urine culture or urine cytologic testing), imaging (multiphase abdominal computed tomography [CT] or intravenous pyelography plus renal ultrasonography), and cystoscopy.[4-6]

Despite these recommendations, the prevalence of urinary tract cancer in the general population is low (0.01%-3%),[1,7-9] translating to a low prior probability of disease for screening. In small populations of patients referred for evaluation of microscopic hematuria, the prevalence of urinary tract cancer has been reported to be 5% to 13%.[10,11] We recently reported findings on a retrospective analysis of a large population of patients who underwent microscopic urinalysis during a 2-year period in which the prevalence of urinary tract cancer was much lower (0.43%).[12] Moreover, the AUA

From the Department of Urology, Southern California Permanente Medical Group, Los Angeles (R.K.L.); Department of Urology, Northwest Permanente Medical Group, Portland, OR (S.F.L.); Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena (S.J.J., J.M.S.); Department of Urology, Hawaii Permanente Medical Group, Honolulu (H.M.L., A.J.M., A.M.A.); and Department of Urology, The Permanente Medical Group, San Rafael, CA (G.N.).

practice recommendations did not perform well in identifying which patients were most likely to have malignant tumors, suggesting that there may be alternative criteria that better identify patients who truly require further evaluation.

On the basis of these findings, we undertook a prospective, observational study within a large managed care organization to determine which patients with asymptomatic microscopic hematuria are at greatest risk for bladder and renal cancer and who would most benefit from urologic evaluation.

PATIENTS AND METHODS

From January 9, 2009, to August 15, 2011, a prospective, observational cohort study was conducted within a large managed care organization (Kaiser Permanente) that provides comprehensive care for members through a capitated health plan. Most health care for members is provided in system-owned medical centers or their affiliated outpatient facilities. A small fraction of emergent and specialty care is obtained from other health care professionals through contractual arrangements or through a claims reimbursement system. All health care encounters are tracked through electronic data systems, with detailed information on diagnoses applied and procedures performed during those encounters, regardless of setting. For outside health care professionals to be reimbursed by the health plan for covered emergent care, claims must be submitted with documentation of the episode of care, and that information is entered into the administrative data systems. Thus, the capture of care provided to Kaiser Permanente members by electronic administrative data is comprehensive.

With agreement from urologists across the program, patients referred to a urologist for evaluation of asymptomatic microscopic hematuria were to be evaluated according to a standard protocol that essentially mirrored the AUA best practice recommendations for hematuria. An electronic data collection tool was developed in which urologists recorded 5 findings for each patient with asymptomatic microhematuria: (1) history of gross hematuria in the past 6 months (yes/no), (2) result of initial imaging, (3) result of secondary imaging (if any), (4) cystoscopy findings, and (5) cause of hematuria. Urinalysis results were stratified as 0 to 3, 4 to 10, 11 to 25, 26 to 50, and more than 50 RBC/HPF. Smoking history, race/ethnicity, and patient demographic characteristics were abstracted from the Kaiser Permanente electronic medical record.

The initial test cohort was composed of members of the Kaiser Permanente health plans in southern California and the Pacific Northwest with hematuria evaluations between January 9, 2009, and October 26, 2010. An independent validation cohort was then assembled from patients from northern California with evaluations from January 9, 2009, through August 15, 2011, and patients in southern California and the Pacific Northwest from October 27, 2010, through August 15, 2011.

Patients were followed passively through their electronic health records for a diagnosis of urothelial or renal cancer. For all patients with a cancer diagnosis, pathologic test results were obtained from electronic health records and pathology reports. Information collected included cancer type, grade, and pathologic stage.

Because not all patients underwent the complete workup, the prevalence of hematuria and urinary tract malignant tumors was estimated for our population.[12] In addition, a separate analysis was performed on patients with microscopic hematuria within the southern California region who were referred to a urologist and did not have data entered into the data collection tool. A 10% random sample of records was reviewed for outcome to evaluate for possible selection bias.

Cohort characteristics were described using percentages. Bivariate associations were assessed using the χ^2 test and logistic regression models. Multivariable logistic regression was used to build a predictive risk model in the initial test cohort. Patient age and degree of hematuria on urinalysis were dichotomized for the risk model, with age in 5-year increments and degree of hematuria cutoffs matching the laboratory's accepted stratification examined to find the most predictive cut point. Statistical significance was not a consideration for adding a factor to the predictive model; rather, improvement in the model's predictive ability, measured by the area under the receiver operating characteristic curve (AUC), was used to identify the strongest

Mayo Clin Proc. ■ XXX 2013;■■(■):1-10 ■ http://dx.doi.org/10.1016/j.mayocp.2012.10.004
www.mayoclinicproceedings.org

model. To simplify the logistic regression model into a risk score, factors with similar parameter estimates were grouped together, and the relative size of the parameter estimates were used to determine relative points in the risk score. Specifically, smoking history, degree of hematuria, and male sex all had relatively small parameter estimates and were each given 1 point, whereas age and history of gross hematuria had parameter estimates averaging approximately 4 times larger and so were given 4 points. The Mantel-Haenszel test for trend was used to test the association of risk score with cancer stage. This risk score was applied to the independent validation cohort. The AUC was then determined for the predictive model.

RESULTS

There were 3,222,699 urinalyses performed in 1,117,542 patients in the test cohort regions from January 9, 2009, to October 26, 2010. Of these patients, 456,674 had microscopic hematuria and 389,207 had 2 positive urinalysis results meeting the threshold for evaluation. During this period, 7778 patients were seen by a urologist for evaluation of asymptomatic microhematuria and 4721 underwent cystoscopy. The details of 2630 of those evaluations were entered into the electronic data collection tool. During the data entry period for the validation cohort, 2,686,014 urinalyses were performed in 1,304,043 patients, of whom 510,623 had a positive urinalysis result and 254,097 had 2 positive urinalysis results. Of 510,623 patients, 12,922 were seen by a urologist, 4118 underwent cystoscopy, and 1784 had their results entered.

The characteristics of the test and validation cohorts are given in Table 1. The test cohort was composed of patients in the southern California region (n=1973) and the Pacific Northwest (n=657). The validation cohort was composed of patients in northern California (n=804), southern California (n=732), and the Pacific Northwest (n=248). Most patients (1529, 58.1% of the test cohort and 1233, 69.1% of the validation cohort) underwent multiphasic abdominal and pelvic CT, with a few patients undergoing intravenous pyelography (503, 19.1% of the test cohort and 172, 9.6% of the validation cohort) plus ultrasonography (795, 30.2% of the test cohort and 399, 22.4% of the validation cohort).

The test and validation cohorts also had some differences in race, with a higher proportion of Hispanic patients having been evaluated in the test cohort.

Smoking history was comparable between the 2 groups. Of note, almost one-third of patients evaluated were younger than 50 years. The degree of microhematuria was slightly higher in the validation cohort, and a significantly higher proportion of patients reported a history of gross hematuria in the past 6 months in the validation cohort than in the test cohort (496/1784, 27.8% vs 379/2630, 14.4%, $P<.001$). The latter may reflect differences in the electronic referral system that exists from primary care to urologic care between the northern and southern California regions.

Pathology reports were reviewed for all patients with cancer diagnoses. A total of 50 cancers (44 bladder and 6 renal) were confirmed in the test cohort and 61 cancers (56 bladder and 5 renal) in the validation cohort. In the test cohort, 5 of 55 neoplasms were benign on the final pathology report, and 1 patient with a 1.7-cm, enhancing renal lesion elected close observation and was counted as having stage T1 cancer. In the validation cohort, 56 of 59 bladder cancers were confirmed as were 5 of 7 renal cancers (2 renal lesions were benign hemorrhagic renal cysts). The overall cancer detection rate was 1.9% in the test cohort (50 of 2630 patients) and 3.4% for the validation cohort (61 of 1784 patients).

Overall, 100 bladder cancers were diagnosed among 4414 patients evaluated (2.3%), and only 11 renal cancers were pathologically confirmed (0.2%).

Among the non-neoplastic findings, the most common findings included urinary stones (713, 16.2%), prostatic bleeding (175, 4.0%), urinary tract infection (102, 2.3%), and glomerular disease (39, 0.9%).

Among the random sample of 158 patients from the 1580 who were referred to a urologist for hematuria in the southern California region during the period of the test cohort but whose results were not entered into the data collection tool, 3 cancers were diagnosed (1.9%), which matches the rate in the test cohort.

In the test cohort, sex, age, history of gross hematuria, smoking history, degree of

TABLE 1. Description of the Study Cohorts

Variable	No. (%) of study participants			*P* value
	Test cohort (n=2630)	Validation cohort (n=1784)	Total (N=4414)	
Region				<.001
Northern California	0	804 (45.1)	804 (18.2)	
Northwest	657 (25.0)	248 (13.9)	905 (20.5)	
Southern California	1973 (75.0)	732 (41.0)	2705 (61.3)	
Sex				<.001
Female	1476 (56.1)	890 (49.9)	2366 (53.6)	
Male	1154 (43.9)	894 (50.1)	2048 (46.4)	
Age (y)				.004
<40	319 (12.1)	180 (10.1)	499 (11.3)	
40-49	509 (19.4)	319 (17.9)	828 (18.8)	
50-59	714 (27.1)	462 (25.9)	1176 (26.6)	
60-69	590 (22.4)	407 (22.8)	997 (22.6)	
≥70	498 (18.9)	416 (23.3)	914 (20.7)	
History of gross hematuria	379 (14.4)	496 (27.8)	875 (19.8)	<.001
Race				<.001
Asian/Pacific Islander	161 (6.1)	108 (6.1)	269 (6.1)	
Black	178 (6.8)	107 (6.0)	285 (6.5)	
Hispanic	255 (9.7)	169 (9.5)	424 (9.6)	
Native American	12 (0.5)	7 (0.4)	19 (0.4)	
Other	162 (6.2)	88 (4.9)	250 (5.7)	
Unknown	842 (32.0)	364 (20.4)	1206 (27.3)	
White	1020 (38.8)	941 (52.7)	1961 (44.4)	
Tobacco use				.34
Missing	0	3 (0.2)	3 (0.1)	
Never	1505 (57.2)	975 (54.7)	2480 (56.2)	
Passive	23 (0.9)	21 (1.2)	44 (1.0)	
Quit	797 (30.3)	569 (31.9)	1366 (30.9)	
Yes	305 (11.6)	216 (12.1)	521 (11.8)	
RBC/HPF on most recent urinalysis				<.001
Missing	190 (7.2)	432 (24.2)	622 (14.1)	
0-3	635 (24.1)	262 (14.7)	897 (20.3)	
4-10	668 (25.4)	409 (22.9)	1077 (24.4)	
11-25	250 (9.5)	186 (10.4)	436 (9.9)	
26-50	341 (13.0)	149 (8.4)	490 (11.1)	
≥51	546 (20.8)	346 (19.4)	892 (20.2)	
2 Positive urinalysis results	1923 (73.1)	924 (51.8)	2847 (64.5)	<.001
Ultrasonography	795 (30.2)	399 (22.4)	1194 (27.1)	<.001
KUB	21 (0.8)	20 (1.1)	41 (0.9)	.27
Intravenous pyelography	503 (19.1)	172 (9.6)	675 (15.3)	<.001
Noncontrast CT	244 (9.3)	169 (9.5)	413 (9.4)	.83
Contrast CT	1285 (48.9)	1064 (59.6)	2349 (53.2)	<.001
Risk group				<.001
Low	875 (33.3)	553 (31.0)	1428 (32.4)	
Moderate	1487 (56.5)	867 (48.6)	2354 (53.3)	
High	268 (10.2)	364 (20.4)	632 (14.3)	
Findings				<.001
Bladder neoplasm	48 (1.8)	59 (3.3)	107 (2.4)	
Renal neoplasm	7 (0.3)	7 (0.4)	14 (0.3)	
Prostate neoplasm	3 (0.1)	2 (0.1)	5 (0.1)	
Glomerular	27 (1.0)	12 (0.7)	39 (0.9)	
Urinary stones	384 (14.6)	329 (18.4)	713 (16.2)	

Continued on next page

Mayo Clin Proc. ■ XXX 2013;■■(■):1-10 ■ http://dx.doi.org/10.1016/j.mayocp.2012.10.004
www.mayoclinicproceedings.org

TABLE 1. Continued

Variable	No. (%) of study participants			*P* value
	Test cohort (n=2630)	Validation cohort (n=1784)	Total (N=4414)	
Findings, continued				
UTI	57 (2.2)	45 (2.5)	102 (2.3)	
Prostatic bleeding	66 (2.5)	109 (6.1)	175 (4.0)	
Contamination	13 (0.5)	3 (0.2)	16 (0.4)	
No cause found	2025 (77.0)	1218 (68.3)	3243 (73.5)	
Pathologically confirmed cancer	50 (1.9)	61 (3.4)	111 (2.5)	.002

CT = computed tomography; KUB = kidneys, ureters, bladder; RBC/HPF = red blood cells per high-power field; UTI = urinary tract infection.

hematuria on the most recent urinalysis, and race were associated with pathologically confirmed cancer. In a multivariable model (Table 2), sex, age, and history of gross hematuria were statistically significantly associated with a cancer finding. Smoking and degree of hematuria were included in the final multivariable model because they increased the model's predictive ability. Race was not included in the final model because of the large number of patients with unknown race/ethnicity and the small numbers in some groups.

The final multivariable model was used to create a Hematuria Risk Index to predict cancer risk. Factors with higher odds ratios in the model (history of gross hematuria and age of 50 years or older) were given 4 points, whereas factors with lower odds ratios (history of smoking, male sex, and >25 RBC/HPF on a recent urinalysis) were given 1 point. On this basis, the Hematuria Risk Index can range from 0 to 11 points. We observed natural breaks in the scores that grouped the patients into low, moderate, and high risk of cancer with 0 to 4 points, 5 to 8 points, and 9 to 11 points, respectively. The AUC for the full multivariable model was 0.850, whereas the AUC was 0.809 for the Hematuria Risk Index and 0.801 for the 3 risk groups (Figure).

When the multivariable logistic regression model from the test cohort was applied in the validation cohort, all 5 factors were predictive of cancer, although there was modest change in the magnitude of the odds ratios of the predictors. However, the overall predictive ability of the Hematuria Risk Index was higher than in the original cohort (AUC = 0.829) and remained nearly as high when compressed to the 3 risk groups (AUC = 0.783).

The Hematuria Risk Index was also associated with cancer stage in the combined cohort (test for trend, *P*=.01, Table 3). All 3 cancers in the low-risk group were stage Ta bladder cancer; 11 of 13 stage T2 and T3 cancers (bladder) were in the high-risk group.

DISCUSSION

In this prospective cohort study, we found that microscopic hematuria is an unreliable indicator of urothelial or renal malignant tumors. An extremely small proportion of patients with microscopic hematuria are subsequently found to have cancer, confirming our previous retrospective results.[12] In fact, most malignant tumors can be identified by a history of gross hematuria, a far more reliable indicator of the need for urologic evaluation and imaging. This finding suggests that a large number of follow-up examinations, which often include radiologic and invasive procedures, could be safely avoided.

Previous studies have identified risk factors that might suggest more serious findings in patients with asymptomatic microscopic hematuria.[7,13] As in other studies, we found that a history of gross hematuria, age, sex, and smoking history were predictive of malignant tumors. The degree of microscopic hematuria, however, was only suggestive of malignant tumors. Our previously reported findings from a retrospective analysis of 156,691 patients with hematuria suggested that low-grade hematuria (<25 RBC/HPF) was not a reliable indicator of the presence of urologic malignant tumors; the overall 3-year incidence of urinary tract cancer was only 0.43%.[12] Mariani et al[3] reported that

TABLE 2. Factors Associated With Cancer Detection in the Test and Validation Cohort[a]

Factor	No. (%) of patients in the test cohort				No. (%) of patients in the validation cohort			
	No cancer (n=2580)	Cancer (n=50)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	No cancer (n=1723)	Cancer (n=61)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Sex								
Female	1464 (99.2)	12 (0.8)	1	1	880 (98.9)	10 (1.1)	1	1
Male	1116 (96.7)	38 (3.3)	4.15 (2.16-7.99)	2.50 (1.22-5.10)	843 (94.3)	51 (5.7)	5.33 (2.69-10.6)	2.93 (1.41-6.09)
Age (y)								
<40	319 (100)	0 (0.0)	0	…[b]	180 (100)	0	0	…
40-49	506 (99.4)	3 (0.6)	1	…	317 (99.4)	2 (0.6)	1	…
50-59	703 (98.5)	11 (1.5)	2.64 (0.73-9.51)	…	453 (98.1)	9 (1.9)	3.15 (0.68-14.7)	…
60-69	573 (97.1)	17 (2.9)	5.00 (1.46-17.2)	…	391 (96.1)	16 (3.9)	6.49 (1.48-28.4)	…
≥70	479 (96.2)	19 (3.8)	6.69 (1.97-22.8)	…	382 (91.8)	34 (8.2)	14.1 (3.36-59.2)	…
Age (y)								
<50	825 (99.6)	3 (0.4)	1	1	497 (99.6)	2 (0.4)	1	1
≥50	1755 (97.4)	47 (2.6)	7.36 (2.29-23.7)	16.3 (2.22-119)	1226 (95.4)	59 (4.6)	11.9 (2.89-48.8)	13.7 (1.86-101)
History of gross hematuria								
No	2232 (99.2)	19 (0.8)	1	…	1269 (98.5)	19 (1.5)	1	1
Yes	348 (91.8)	31 (8.2)	10.5 (5.85-18.7)	9.89 (5.20-18.8)	454 (91.5)	42 (8.5)	6.16 (3.55-10.7)	4.30 (2.27-8.14)
Race								
Asian/Pacific Islander	160 (99.4)	1 (0.6)	0.21 (0.03-1.58)	…	104 (96.3)	4 (3.7)	0.73 (0.26-2.07)	…
Black	169 (94.9)	9 (5.1)	1.82 (0.85-3.91)	…	102 (95.3)	5 (4.7)	0.93 (0.36-2.40)	…
Hispanic	251 (98.4)	4 (1.6)	0.54 (0.19-1.56)	…	166 (98.2)	3 (1.8)	0.34 (0.11-1.12)	…
Native American	11 (91.7)	1 (8.3)	3.11 (0.39-24.9)	…	7 (100)	0	0	…
Other	160 (98.8)	2 (1.2)	0.43 (0.10-1.81)	…	87 (98.9)	1 (1.1)	0.22 (0.03-1.60)	…
Unknown	838 (99.5)	4 (0.5)	0.16 (0.06-0.47)	…	363 (299.7)	1 (0.3)	0.05 (0.01-0.38)	…
White	991 (97.2)	29 (2.8)	1	…	894 (95)	47 (5)	1	…
Tobacco use								
Missing	…	…	…	…	3 (0.2)	0	…	…
Never	1486 (98.7)	19 (1.3)	1	…	956 (98.1)	19 (1.9)	1	…
Passive	23 (100)	0	0	…	20 (95.2)	1 (4.8)	2.52 (0.32-19.7)	…
Quit	773 (97.0)	24 (3.0)	2.43 (1.32-4.46)	…	536 (94.2)	33 (5.8)	3.10 (1.74-5.50)	…
Current	298 (97.7)	7 (2.3)	1.84 (0.77-4.41)	…	208 (96.3)	8 (3.7)	1.94 (0.84-4.48)	…
Ever used tobacco								
Missing	…	…	…	…	3 (0.2)	0	…	…
No	1486 (98.7)	19 (1.3)	1	1	956 (98.1)	19 (1.9)	1	1
Yes	1094 (97.2)	31 (2.8)	2.22 (1.25-3.94)	1.48 (0.78-2.81)	764 (94.8)	42 (5.2)	2.77 (1.60-4.79)	1.88 (1.01-3.53)
RBC/HPF on most recent urinalysis								
Missing	185 (97.4)	5 (2.6)	…	…	422 (24.5)	10 (16.7)	…	…
0-3	631 (99.4)	4 (0.6)	1	…	255 (97.3)	7 (2.7)	1	…
4-10	658 (98.5)	10 (1.5)	2.40 (0.75-7.68)	…	404 (98.8)	5 (1.2)	0.45 (0.14-1.44)	…
11-25	241 (96.4)	9 (3.6)	5.89 (1.80-19.3)	…	181 (997.3)	5 (2.7)	1.01 (0.32-3.24)	…
26-50	334 (97.9)	7 (2.1)	3.31 (0.96-11.4)	…	144 (96.6)	5 (3.4)	1.26 (0.39-4.06)	…
≥51	531 (97.3)	15 (2.7)	4.46 (1.47-13.5)	…	317 (91.6)	29 (8.4)	3.33 (1.44-7.73)	…
At least 25 RBC/HPF on recent urinalysis								
No	592 (98.2)	11 (1.8)	1	1	484 (98)	10 (2)	1	1
Yes	1807 (98.2)	34 (1.8)	1.01 (0.51-2.01)	1.26 (0.62-2.57)	817 (95.2)	41 (4.8)	2.43 (1.21-4.89)	2.29 (1.12-4.71)
Bladder neoplasm	4 (8.3)	44 (91.7)	…	…	3 (5.1)	56 (94.9)	…	…
Renal neoplasm	1 (14.3)	6 (85.7)		…	2 (28.6)	5 (71.4)		
Risk group								
Low	872 (99.7)	3 (0.3)	1	…	553 (3100)	0	0	…
Moderate	1471 (98.9)	16 (1.1)	3.16 (0.92-10.9)	…	845 (97.5)	22 (2.5)	1	…
High	237 (88.4)	31 (11.6)	38.0 (11.5-125)	…	325 (89.3)	39 (10.7)	4.61 (2.69-7.89)	…

[a]CI = confidence interval; OR = odds ratio; RBC/HPF = red blood cells per high-power field.

[b]Ellipses indicate data not available/applicable.

Mayo Clin Proc. ■ XXX 2013;■■(■):1-10 ■ http://dx.doi.org/10.1016/j.mayocp.2012.10.004
www.mayoclinicproceedings.org

because of the intermittent nature of hematuria, more than one positive specimen should be obtained before recommending full evaluation. Furthermore, only high-grade hematuria (>50 RBC/HPF or gross hematuria) was a clear risk factor, and lower degrees of hematuria at any level or frequency were not reliable indicators of significant findings. In their series of 1000 patients, the risk of finding a genitourinary tract malignant tumor was 6.36 times higher in patients with a history of gross hematuria, which is similar to our odds ratio of 7.2 in our combined cohorts. This finding has been corroborated in other reports, yet recommendations for evaluation have remained largely unchanged for 20 years.[14] In our study, the odds of cancer detection for patients with 2 positive urinalysis results was not significantly different from that of patients with only 1 positive urinalysis result (P=.89, AUC = 0.504). Thus, a history of gross hematuria may be a far more reliable indicator of urologic malignant tumors than random urinalysis screening with any degree of microscopic hematuria.

Prior studies have suggested an age cutoff of 40 years, particularly for women, to stratify as very low risk.[4,5] The 2012 AUA asymptomatic microscopic hematuria guideline now recommends evaluation of persons as young as 35 years.[6,15-19] Our study suggests that a designation of low risk may be safely extended to 50 years of age; however, risk of urinary tract malignant tumors still predominates in males.

A number of nontrivial risks are associated with the workup of microscopic hematuria. Radiation exposure due to unnecessary CT is a known and likely preventable risk.[20] Brenner and Hall[21] reported that up to 2% of future malignant tumors might be iatrogenic due to CT radiation exposure. A 0.4% risk of cancer due to CT radiation was reported, with the highest risk in patients younger than 40 years. In addition, published studies on CT exposure consistently report higher exposure rates for women vs men. More selective criteria have been proposed with respect to CT to reduce radiation risk in younger patients for other types of cancer screening.[22] In the evaluation of microscopic hematuria, intravenous pyelography plus renal ultrasonography has been recommended to reduce radiation exposure, yet achieve some measure of surveillance, albeit at lower diagnostic resolution.[13,22] Serious adverse events are rare with cystoscopy; however, urinary tract infection and sepsis have been reported.[3] Taken together, these risks necessitate a sizable and demonstrable benefit from the workup of microscopic hematuria. Unfortunately, no algorithm has yet been recommended to improve the existing guideline.[23]

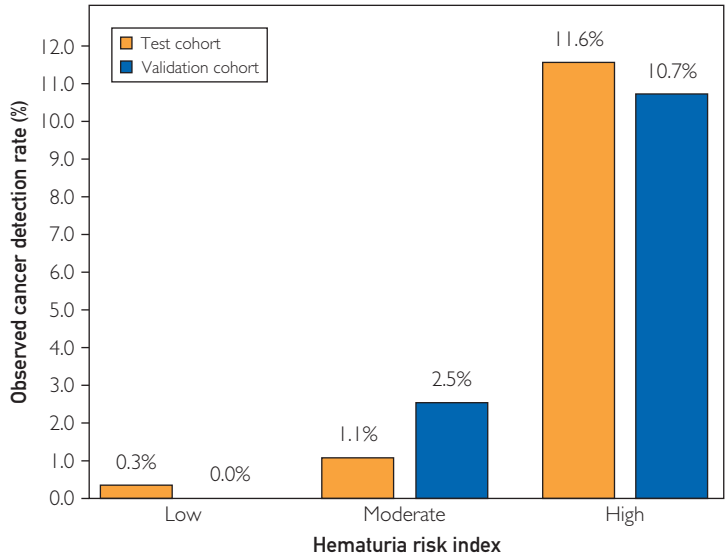

FIGURE. Comparison of cancer detection rates in test and validation cohorts.

For malignant findings, the incidence of renal cancer was extremely low in our study (0.3%), and no ureteral or transitional cell carcinomas of the upper urinary tract were identified in either cohort. On the basis of prior screening studies, microscopic hematuria does not appear to be predictive of renal cancer. In the report by Wolf,[24] a screening study of more than 6000 individuals 50 to 79 years old, the incidence of pathologically confirmed renal cancer was similarly low (0.33%).[25]

Although the main focus of the evaluation of patients with asymptomatic microscopic hematuria is to detect malignant tumors, microscopic hematuria can also be associated with other nonmalignant conditions, including renal parenchymal and glomerular diseases, urolithiasis, and prostatic bleeding. Indeed, our evaluations identified clinically important nonmalignant causes of hematuria. However,

TABLE 3. Final Pathologic Classification of Cancers (Combined Cohorts)[a,b]

Hematuria risk index	Tis (n=4)	Ta (n=58)	T1 (n=36)	T2 (n=10)	T3 (n=3)	Total (N=111)
0-4 (Low)	0	3 (100)	0	0	0	3
5-8 (Moderate)	2 (5.3)	19 (50.0)	15 (39.5)	2 (5.3)	0	38
9-11 (High)	2 (2.9)	36 (51.4)	21 (30.0)	8 (11.4)	3 (4.3)	70

[a]Values are presented as No. (percentage).

[b]Ten patients (4 high risk, 6 moderate risk) had no cancer found on final pathologic examination. One high-risk patient had no pathologic evidence of cancer, but clinical evidence pointed to Ta renal cancer.

only a small proportion (1%) of patients were found to have glomerular disease, likely because of the proper hematuria evaluation by primary care physicians in our system. Our guidelines mirror generally accepted recommendations to refer patients for nephrologic evaluation in the presence of hematuria with associated renal insufficiency, proteinuria, hypertension, or dysmorphic red blood cells. Likewise, few patients were found to have concomitant urinary tract infection (2.7%) because guidelines recommend repeated urinalysis testing after adequate treatment of urinary tract infection. None of the nonmalignant findings identified would have required multiphasic abdominal or pelvic CT to make the appropriate diagnosis.

This study has several potential limitations that should be taken into consideration when interpreting our results. Not all urologists participated in the data collection; therefore, not all patients who may have undergone microhematuria evaluation were included in either cohort, and these patients may be systematically different from those who were included. Data were entered for only 50% of patients who underwent cystoscopy for microhematuria during the period. The similarity in cancer diagnosis rates among those followed up according to plan vs not, however, suggests that this likely played only a small role. In addition, few sizeable differences were identified between the 2 large cohorts, which varied in geography and urologists. All study participants were from the West Coast of the United States (California and Oregon), and the Hematuria Risk Index may require assessment before recommending use elsewhere because variations in race, smoking habits, and carcinogenic exposure may influence index performance. Demographic variation in referral by region may have played a role in the modest differences seen in the cancer detection rates between the test and validation cohorts (1.9% vs 3.4%). The test cohort was younger on average and had a higher percentage of female patients referred for evaluation. In addition, nearly twice as many patients had a history of gross hematuria in the validation cohort compared with the test cohort.

Because the recording of the specific patient data was voluntary and the study crossed different health plan regions and years, several sensitivity analyses were performed to determine whether the results were consistent. To further address potential selection bias, we examined the patients of physicians who entered at least 50 cases during the study because we believed these physicians were most likely to enter all of their patients and not just the "interesting" ones. In the initial cohort this group comprised 62% of patients and 65% of those with cancer, and the Hematuria Risk Index also predicted cancer detection in the total cohort (AUC = 0.811 in this subset vs 0.809 in the entire cohort). In the validation cohort, 51% of patients, comprising 52% of those with cancer, were identified by physicians entering data on at least 50 patients. The Hematuria Risk Index was strongly predictive in this group (AUC = 0.823 vs 0.833 in the full cohort). Subgroups by region were also examined, and although some differences were found in rates of cancer and distribution of predictors, the risk score predicted similarly well across regions, with AUCs ranging from 0.789 in the Pacific Northwest validation cohort to 0.866 in the southern California validation cohort. In all regions, the low-risk group had a less than 0.5% risk of cancer, whereas the high-risk group had a greater than 10% risk.

This study was based on real-world outpatient referrals from primary care physicians in an integrated care setting. All patients were referred with asymptomatic microscopic hematuria. No patients underwent evaluation on the basis of dipstick urinalysis results,

Mayo Clin Proc. ■ XXX 2013;■■(■):1-10 ■ http://dx.doi.org/10.1016/j.mayocp.2012.10.004
www.mayoclinicproceedings.org

eliminating potential overdetection bias.[10,11] Reflective of historical referrals and what we believe is typical from primary care physicians, most patients met the criteria of 2 of 3 positive urinalysis results of 3 or more RBC/HPF. All patients specifically referred for gross hematuria were excluded from this study. Interestingly, despite the fact that all patients referred had a history of asymptomatic microscopic hematuria, a large number of those with gross hematuria did not have a history of gross hematuria in the past 6 months documented by their primary care physicians. This finding, combined with the importance of this risk factor in predicting urinary tract malignant tumors, highlights the importance of obtaining a detailed history from all patients identified as having microscopic hematuria, specifically asking if they have ever seen blood in their urine. On the basis of our findings, the risk of identifying a urinary tract cancer in anyone younger than 50 years without a history of gross hematuria is close to zero.

Since the 2001 AUA guideline was published and recently updated, the predominant imaging modality to screen for microscopic hematuria has become multiphasic abdominal and pelvic CT, in which the risk of carcinogenic ionizing radiation is inversely related to the age at exposure. In 2009, the Canadian Urologic Association revised their recommendations for the evaluation of patients with asymptomatic microscopic hematuria. Citing limited evidence and radiation (and intravenous contrast) risk, they now recommend ultrasonography as the imaging test of first choice.[26] Others, including the Dutch Association of Urology, are following a similar risk-based strategy in an attempt to minimize radiation exposure risk in patients with hematuria who have a low likelihood of development of malignant tumors.[27] Recently, the AUA published updated guidelines for the diagnosis, evaluation, and follow-up of asymptomatic microscopic hematuria in adults. The new guidelines recommend a thorough urologic evaluation of all asymptomatic patients 35 years and older who have a single urinalysis result with 3 RBC/HPF or more, consisting of multiphasic CT urography and cystoscopy. Of the 19 guideline statements, none cite evidence strength above grade C. Furthermore, the AUA cited the need to report strong observational research because asymptomatic microhematuria is a common sign in which widespread screening takes place in the absence of good evidence.[6] This recommendation is particularly important because microscopic hematuria is ubiquitous in the general population. Fortunately, only a small percentage of patients with asymptomatic microscopic hematuria are referred for diagnostic evaluation.[7,10] In our patient population, which represents a real-world general health care setting, less than 2.1% of patients in the test cohort who had 2 positive urinalysis results and 1.7% who had 1 positive urinalysis result were referred for diagnostic evaluation. However, as electronic health records with computerized decision support become more commonplace, it is possible that many more asymptomatic patients with microscopic hematuria will be identified and referred, which could lead to many more potentially unnecessary evaluations unless different screening guidelines are implemented. To this end, balanced strategies that weigh risk vs benefit may lead to better population outcome.

CONCLUSION

These data suggest that microscopic hematuria is an unreliable indicator of urinary tract malignant tumors. Patients with microscopic hematuria younger than 50 years and with no history of gross hematuria may not benefit from further evaluation and therefore could avoid unnecessary risk from radiation exposure and invasive endoscopy. These findings may be used to simplify referral guidelines for evaluation in asymptomatic patients with microscopic hematuria and reduce the number of unnecessary evaluations.

Abbreviations and Acronyms: **AUA** = American Urological Association; **AUC** = area under the receiver operating characteristic curve; **CT** = computed tomography; **RBC/HPF** = red blood cells per high-power field

Grant Support: This study was funded from internal infrastructure from the Department of Research and Evaluation, Kaiser Permanente Southern California.

Correspondence: Address to Steven J. Jacobsen, MD, PhD, Kaiser Permanente Southern California, 100 S Los Robles, Second Floor, Pasadena, CA 91101 (Steven.J.Jacobsen@kp.org).

REFERENCES

1. Mohr DN, Offord KP, Owen RA, et al. Asymptomatic microhematuria and urologic disease: a population-based study. *JAMA*. 1986;256(2):224-229.

2. Freni SC, Freni-Titulaer LW. Microhematuria found by mass screening of apparently healthy males. *Acta Cytol*. 1977;21(3):421-423.
3. Mariani AJ, Mariani MC, Macchioni C, et al. The significance of adult hematuria: 1,000 hematuria evaluations including a risk-benefit and cost-effectiveness analysis. *J Urol*. 1989;141(2):350-355.
4. Grossfeld GD, Litwin MS, Wolf JSJ, et al. Evaluation of asymptomatic microscopic hematuria in adults: the American Urological Association best practice policy—part I: definition, detection, prevalence, and etiology. *Urology*. 2001;57(4):599-603.
5. Grossfeld GD, Wolf JSJ, Litwin MS, et al. Asymptomatic microscopic hematuria in adults: summary of the AUA best practice policy recommendations. *Am Fam Physician*. 2001;63(6):1145-1154.
6. Davis R, Jones JS, Barocas DA, et al. Diagnosis, evaluation, and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. Paper presented at: American Urologic Association Meeting; May 23, 2012; Atlanta, Georgia.
7. Sutton JM. Evaluation of hematuria in adults. *JAMA*. 1990;263(18):2475-2480.
8. Thompson IM. The evaluation of microscopic hematuria: a population-based study. *J Urol*. 1987;138(5):1189-1190.
9. Murakami S, Igarashi T, Hara S, et al. Strategies for asymptomatic microscopic hematuria: a prospective study of 1,034 patients. *J Urol*. 1990;144(1):99-101.
10. Fracchia JA, Motta J, Miller LS, et al. Evaluation of asymptomatic microhematuria. *Urology*. 1995;46(4):484-489.
11. Carson CC III, Segura JW, Greene LF. Clinical importance of microhematuria. *JAMA*. 1979;241(2):149-150.
12. Jung H, Gleason JM, Loo RK, et al. Association of hematuria on microscopic urinalysis and risk of urinary tract cancer. *J Urol*. 2011;185(5):1698-1703.
13. Loo R, Whittaker J, Rabrenivich V. National practice recommendations for hematuria: how to evaluate in the absence of strong evidence? *Perm J*. 2009;13(1):37-46.
14. Chou R, Dana T. Screening adults for bladder cancer: a review of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2010;153(7):461-468.
15. Jones DJ, Langstaff RJ, Holt SD, et al. The value of cystourethroscopy in the investigation of microscopic haematuria in adult males under 40 years: a prospective study of 100 patients. *Br J Urol*. 1988;62(6):541-545.
16. Wu JM, Williams KS, Hundley AF, et al. Microscopic hematuria as a predictive factor for detecting bladder cancer at cystoscopy in women with irritative voiding symptoms. *Am J Obstet Gynecol*. 2006;194(5):1423-1426.
17. Bard RH. The significance of asymptomatic microhematuria in women and its economic implications: a ten-year study. *Arch Intern Med*. 1988;148(12):2629-2632.
18. Abbaszadeh S, Taheri S, Nourbala MH. Bladder tumor in women with microscopic hematuria: an Iranian experience and a review of the literature. *Adv Urol*. 2009:231861.
19. Messing EM, Young TB, Hunt VB, et al. Home screening for hematuria: results of a multiclinic study. *J Urol*. 1992;148(2, pt 1):289-292.
20. Kalra MK, Maher MM, Toth TL, et al. Strategies for CT radiation dose optimization. *Radiology*. 2004;230(3):619-628.
21. Brenner DJ, Hall EJ. Computed tomography: an increasing source of radiation exposure. *N Engl J Med*. 2007;357(22):2277-2284.
22. O'Regan KN, O'Connor OJ, McLoughlin P, et al. The role of imaging in the investigation of painless hematuria in adults. *Semin Ultrasound CT MR*. 2009;30(4):258-270.
23. Feldstein MS, Hentz JG, Gillett MD, et al. Should the upper tracts be imaged for microscopic haematuria? *BJU Int*. 2005;96(4):612-617.
24. Wolf JS Jr. Evaluation and management of solid and cystic renal masses. *J Urol*. 1998;159(4):1120-1133.
25. Koeneman KS, Cote WL, Martin DJ, et al. Renal screening ultrasound in an older population with pathologic correlation [abstract 1276]. *J Urol*. 1997;157:327.
26. Wollin T, Laroche B, Psooy K. Canadian guidelines for the management of asymptomatic microscopic hematuria in adults. *Can Urol Assoc J*. 2009;3(1):77-80.
27. van der Molen AJ, Hovius MC. Hematuria: a problem-based imaging algorithm illustrating the recent Dutch guidelines on hematuria. *AJR Am J Roentgenol*. 2012;198(6):1256-1265.

Mayo Clin Proc. ■ XXX 2013;■■(■):1-10 ■ http://dx.doi.org/10.1016/j.mayocp.2012.10.004
www.mayoclinicproceedings.org