# EVALUATION OF HEMATURIA AND PROTEINURIA POSITIVITY IN RELATION TO AGEING IN 6,651 APPARENTLY HEALTHY MEN AND WOMEN

Tomoyuki Shimabukuro[1] and Katsusuke Naito[2]

[1]*The Department of Urology, Ube Industries Central Hospital*

[2]*The Department of Urology, Graduate School of Medicine, Yamaguchi University*

We examined the positivity of hematuria and proteinuria in relation to ageing in 6,651 apparently healthy persons (2,556 women and 4,095 men) who underwent multiphasic health screening in our Medical Checkup Center. Commercially available dipsticks were used. The time from urine collection to dipstick analysis was within 60 minutes. The mean age of women was 48.2 years (range 10 to 82) and that of men was 49.9 years (range 7 to 89). Approximately 30.1, 1.5, and 0.7% of the women had hematuria, proteinuria, and hematoproteinuria, respectively; and 11.4, 4.0, 1.5% of the men had the corresponding urine abnormalities, respectively. Hematuria was 2.6 times more common in women than in men, and proteinuria was 2.7 times more common in men than in women. The positivity of hematuria increased linearly with age in women (Rs=0.943, $P$=0.0350). On the other hand, the positivity of proteinuria or hematoproteinuria was not correlated with age ($P$=0.8386 and $P$=0.0639, respectively). In men, the positivity of hematuria or hematoproteinuria was not correlated with age ($P$=0.0845 and $P$=0.0845, respectively). However, the positivity of proteinuria in those more than 30-year age group increased linearly with age (Rs=1.000, $P$=0.0455). The true meaning of such gender- and/or age-related differences in urinary abnormalities remains to be determined.

(Hinyokika Kiyo **53** : 783–788, 2007)

**Key words** : Hematuria, Proteinuria, Apparently healthy persons, Both sexes, Ageing

## INTRODUCTION

Hematuria (blood in the urine) can originate from any site along the urinary tract and, whether gross or microscopic, may be a sign of serious underlying disease, including malignancy. Most physicians agree that the presence of gross hematuria warrants a thorough diagnostic evaluation to determine its underlying cause. In contrast, microscopic hematuria is an incidental finding that is discovered as part of a routine examination of patients or mass urinalysis screening in the health examination program. The decision to initiate an evaluation in a person with asymptomatic microscopic hematuria and the type of evaluation are still matters of considerable debate[1–3].

As fundamental data for the arguments, we determined the incidence of urinary abnormalities with age by dipstick chemical urinalysis in a screening population of 6,651 apparently healthy persons.

## PERSONS AND METHODS

*Persons*

Between April 2005 and March 2006, the apparently healthy subjects who underwent multiphasic health screening in our Medical Checkup Center of Ube Industries Central Hospital were analyzed with regard to the proportion of hematuria and proteinuria as related to gender and ageing. The institutional review board approved the study because these persons were anonymous, and they were requested to disclose their age, sex and the data of screening urinalysis only. In the present study, therefore, the data and health screening could not be linked together, and no information could be obtained on past and concurrent disease or medications.

All participants were Japanese and lived in or around Ube city.

*Dipstick Urinalysis Screening*

Persons were instructed to obtain a clean-catch midstream urine specimen. Commercially available dipsticks were used (Multistix SG-L, Bayer Medical Ltd, Great Britain). The time from urine collection to dipstick analysis were within 60 minutes.

*Terminology*

We followed the Guideline of Hematuria Diagnosis by the Japanese Urological Association[4].

We defined positive hemoglobin and protein as 1+ or greater by the dipstick urinalysis test.

*Statistical Analysis*

The differences between women and men in the positive hemoglobin and protein groups were analyzed by the Mann-Whitney's $U$ test. The differences between each age group by gender in these positivities were also analyzed by the Mann-Whitney's $U$ test. Spearman's correlation coefficients by rank were calculated to examine the linear trends.

Results with a probability ($P$) value of less than 0.05 were considered statistically significant.

## RESULTS

*Persons*

Between April 2005 and March 2006, 9,140 apparently healthy persons (3,699 women and 5,441 men) visited the Medical Checkup Center of Ube Industries Central Hospital for medical checkups, and we enrolled 6,651 of them who has urine evaluated by the Dipstick test in this study. There were 2,556 (38.4%) women, and 4,095 (61.6%) men. The mean age of the women was 48.2 years (range 10 to 82) and that of the men was 49.9 years (range 7 to 89). In both sexes, persons in the 6th decade represented the most numerous age group (Fig. 1).

*Cost for Dipstick Urinalysis Screening*

The cost for a Dipstick-urinalysis-screening is $3.5 in Japan.

*Occult Hematuria in Both Sexes*

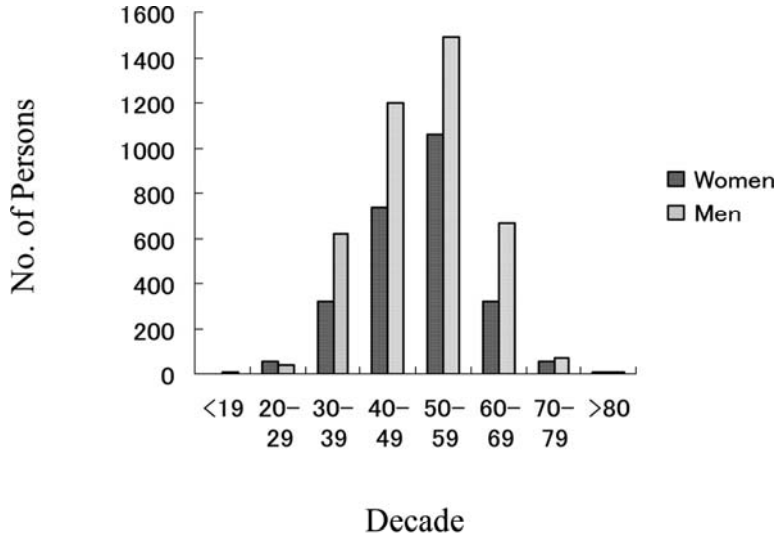


**Fig. 1.** Age distribution of the female and male study participants.

**Table 1.** Urine blood positive grade distributions according to each decade in apparently healthy women and men. All *P* values for women versus men of same age group.

| Status by age | Women n (%) | | | | Men n (%) | | | |
|---|---|---|---|---|---|---|---|---|
| | n | 1+ | 2+ | 3+ | n | 1+ | 2+ | 3+ |
| ≤29 | 56 | 3 ( 5.4) | 2 ( 3.6) | 4 ( 7.1) | 42 | 1 ( 2.4) | 1 (2.4) | 1 (2.4) |
| 30–39*1 | 324 | 23 ( 7.1) | 19 ( 5.9) | 34 (10.5) | 618 | 19 ( 3.1) | 17 (2.8) | 4 (0.6) |
| 40–49*2 | 736 | 83 (11.3) | 73 ( 9.9) | 67 ( 9.1) | 1, 199 | 66 ( 5.5) | 42 (3.5) | 18 (1.5) |
| 50–59*3 | 1,055 | 177 (16.8) | 109 (10.3) | 57 ( 5.4) | 1,490 | 124 ( 8.3) | 41 (2.8) | 32 (2.1) |
| 60–69*4 | 325 | 56 (17.2) | 27 ( 8.3) | 16 ( 4.9) | 666 | 57 ( 8.6) | 30 (4.5) | 5 (0.8) |
| 70–79*5 | 55 | 8 (14.6) | 8 (14.6) | 2 ( 3.6) | 71 | 5 ( 7.0) | 2 (2.8) | 2 (0.8) |
| ≥80 | 5 | 2 (40.0) | — | — | 9 | 1 (11.1) | — | — |
| Total | 2,556 | 352 (13.8) | 238 ( 9.3) | 180 ( 7.0) | 4,095 | 273 ( 6.7) | 133 (3.2) | 62 (1.5) |

Key : *1, *2, *3 and *4 ; $P<0.0001$, *5 ; $P=0.0071$.

**Table 2.** Urine protein positive grade distributions according to each decade in apparently healthy women and men. All *P* values for women versus men of same age group.

| Status by age | Women n (%) | | | | Men n (%) | | | |
|---|---|---|---|---|---|---|---|---|
| | n | 1+ | 2+ | 3+ | n | 1+ | 2+ | 3+ |
| ≤29 | 56 | 1 ( 1.8) | — | 1 (1.8 ) | 42 | 2 (4.8) | — | — |
| 30–39 | 324 | 4 ( 1.2) | 1 (0.3) | — | 618 | 5 (0.8) | 5 (0.8) | — |
| 40–49*1 | 736 | 10 ( 1.4) | — | — | 1,199 | 22 (1.8) | 12 (1.0) | 3 (0.3) |
| 50–59*2 | 1,055 | 11 ( 1.0) | 5 (0.5) | — | 1,490 | 40 (2.7) | 20 (1.3) | 9 (0.6) |
| 60–69*3 | 325 | 3 ( 0.9) | 2 (0.6) | — | 666 | 30 (4.5) | 6 (0.9) | 2 (0.3) |
| 70–79 | 55 | — | 1 (1.8) | — | 71 | 4 (5.6) | 3 (4.2) | — |
| ≥80 | 5 | 1 (20.0) | — | — | 9 | — | — | — |
| Total | 2,556 | 30 ( 1.2) | 9 (0.4) | 1 (0.04) | 4,095 | 103 (2.5) | 46 (1.1) | 14 (0.3) |

Key : *1 ; $P=0.0203$, *2 and *3 ; $P<0.0001$.

Table 1 shows urine blood positive grade distributions according to each decade in both sexes. Approximately 30.1% of the women and 11.4% of the men had positive urine blood. Hematuria was 2.6 times more common in women than in men. This positivity showed a statistically significant difference between women and men ($P<0.0001$).

Except for the under 30 and over 80, women had significantly higher positive urine blood in each decade than men.

*Urine Protein in Both Sexes*

Table 2 shows urine protein positive grade distributions according to each decade in both sexes. Approximately 1.5% of the women and 4.0% of the men had positive urine protein. Proteinuria was 2.7 times more common in men than in women. This positivity showed a statistically significant difference between the women and men ($P<0.0001$).

Except for the under 40 and over 70, men had significantly higher positive urine protein in each decade than women.

*Hematoproteinuria in Both Sexes*

Table 3 shows the distribution of persons with hematoproteinuria according to each decade in both sexes. In each decade, approximately 0.9% of women and 1.1% of men had hematoproteinuria.

*Relationship between Age and the Positivity of Urinary Abnormality*

Fig. 2 shows the relationship between the age at urine test and the positivity of abnormal urine findings in both sexes.

In women, the positivity of hematuria increased linearly with age, from 16.1% in the under 30 to 33.3% in those over 70 (Rs=0.943, $P=0.0350$). On the other hand, the positivity of proteinuria or hematoproteinuria was not correlated with age ($P=0.8386$ and $P=0.0639$, respectively).

In men, the positivity of hematuria or hematoproteinuria was not correlated with age ($P=0.0845$ and $P=0.0845$, respectively). But the positivity of proteinuria in those over 30 increased linearly with age, from 1.6% in the 30 to 39-year age group to 8.8% in those over 70 (Rs=1.000, $P=0.0455$).

**Table 3.** Hematoproteinuria distributions according to each decade in apparently healthy women and men

| Status by age | Women | | | Men | | |
|---|---|---|---|---|---|---|
| | n | n (%) | 95% CI (%) | n | n (%) | 95% CI (%) |
| ≤29 | 56 | 1 (1.8) | −1.7–5.3 | 42 | — | — |
| 30–39 | 324 | 4 (1.2) | 0.0–2.4 | 618 | 3 (0.5) | —0.6–1.1 |
| 40–49 | 736 | 5 (0.7) | 0.1–1.3 | 1,199 | 14 (1.2) | 0.6–1.8 |
| 50–59 | 1,055 | 6 (0.6) | 0.2–1.0 | 1,490 | 35 (2.3) | 1.5–3.1 |
| 60–69 | 325 | 3 (0.9) | −0.1–1.9 | 666 | 10 (1.5) | 0.5–2.5 |
| 70–79 | 55 | — | — | 71 | 1 (1.4) | −1.3–4.1 |
| ≥80 | 5 | — | — | 9 | — | — |
| Total | 2,556 | 19 (0.7) | 0.3–1.1 | 4,095 | 63 (1.5) | 1.1–1.9 |

Key: 95% CI=95% confidence interval.

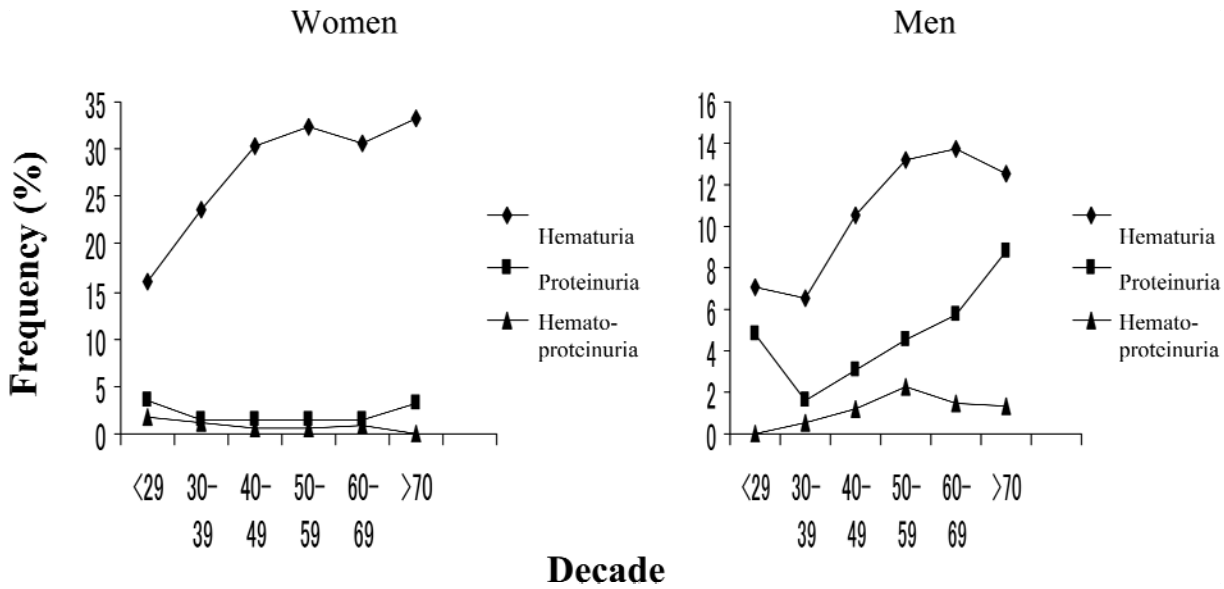


**Fig. 2.** Relationship between age and the frequency of urinary abnormality in women and men.

## DISCUSSION

The simplest way to detect microscopic hematuria and/or proteinuria is with a urinary dipstick. Hemoglobin catalyzes an oxidation reaction between substances on the dipstick, resulting in a color change that indicates the presence of hematuria. Urinary dipsticks have been very useful in the detection of asymptomatic hematuria, with a sensitivity of 91% to 100%[1,5,6]. The dipstick tests for protein use a tetrabromophenol blue indicator system. The dipstick is highly accurate, detecting albuminuria at levels of 0.3 g/l. Sensitivities and specificities for albuminuria are greater than 99% in the laboratory setting[7]. Recently, a guideline of hematuria diagnosis was established by the Japanese Urological Association[4]. The recommended definition of positive dipstick test for hemoglobin is 1+ (hemoglobin 0.06 mg/ml) or more and microscopic hematuria is 5 or more red blood cells/high-power microscopic field. Following the guideline, we determined the incidence of hematuria and/or proteinuria indirectly diagnosed by dipstick examination of urine from apparently healthy persons visiting our Medical Checkup Center.

A potential limitation of our study was that it was not a population-based study, and the enrolled subjects were derived from a health screening population. The proportions of participants under 30 and over 70 were very small, and thus the present study may not reflect the general prevalence of hematuria and proteinuria in the entire Japanese population. Nevertheless we believe that the present study still permitted a comparison of the incidence of hematuria and proteinuria between women and men in the same age group.

Iseki and colleagues reported from their 107, 192 subjects mass screening study that the incidence of hematuria in women was 11.0% and that in men was 2.8%[8]. Mohr and colleagues also reported that the overall prevalence of asymptomatic microhematuria was 12.7% in the general population of women age 55 and older and 13.2% in that of men age 35 and older[9]. Woohlhandler and colleagues reviewed five populations ranging from 1,000 to 95,200 persons[1]. The estimated prevalence of asymptomatic microscopic hematuria varied in these studies from 0.19% to 16.1%. From the present study, approximately 30.1% of the women and 11.4% of the men had positive urine blood, and the women had a higher prevalence than the men ($P<0.0001$). One of the reasons of our higher prevalence of hematuria, especially in women, came from the relatively higher incidence of menstrual-aged women in this study. Contamination of the urine by menstrual blood results in false-positive hematuria. Other causes of false positive results include dehydration with resultants urine of high specific gravity as a result of the increased concentration of erythrocytes and hemoglobin, exercise, which can increase the number of erythrocytes and ingestion of vitamin C, which inhibits peroxidase reactions.

The increased positivity of microhematuria with age might be explained by the higher normal values of red blood cells (RBC) excretion in elderly persons and the increased prevalence of urothelial malignancies with age[10]. In women, the positivity of hematuria increased linearly with age (Fig. 2). In a population-based study, Mohr and colleagues reported that the frequency of serious urologic disease in patients with asymptomatic microhematuria was 2.3%, and only 0.5% had bladder or renal cell carcinoma[9]. They concluded that the positive predictive value of hematuria in asymptomatic patients is too low to warrant routine screening. In contrast, Messing and colleagues found that 26% of men with at least one positive heme dipstick definitely had significant urinary tract lesions[6].

Woohlhandler and colleagues reviewed four population-based studies of asymptomatic proteinuria in adults ranging from 1,456 to 36,147[1]. The estimated prevalence of asymptomatic proteinuria varied in these studies from 0.38% to 1.85%. Iseki and colleagues reported that the incidence of proteinuria in women was 3.5% and that in men was 4.7%[8]. In the present study, approximately 1.5% of the women and 4.0% of the men were positive for urine protein, and the men had a higher prevalence than the women ($P<0.0001$). The positivity of proteinuria increased linearly with age in men (Fig. 2). Such gender difference in proteinuria might reflect the differences in the preponderance of primary glomerular disease, which occurs more frequently in men than women, in the involvement of testosterone and other sex-related hormones[11], and responsibility of acquired obstruction due to prostatic disease[12].

Iseki and colleagues reported that the incidence of hematoproteinuria in women was 1.3% and that in men was 0.7%, and that hematoproteinuria was the most potent predictor of end-stage renal disease[8]. Also in this study, approximately 0.7% of women and 1.5% of men had hematoproteinuria. The results indicated that approximately 1% of apparently healthy persons had hematoproteinuria, and combined with proteinuria, the prevalence of apparently healthy persons with urine protein is approximately 3 to 5%. Proteinuria of 1+ or greater on dipstick urinalysis should prompt a 24-hour urine collection to quantitate the degree of proteinuria. A total protein excretion of greater than 0.5 g/24 hr, particularly if the protein excretion is increasing and/or persistent, should prompt a more extensive evaluation for renal parenchymal disease. A renal biopsy is recommended for diagnosis, prognosis and guidance of therapy[13].

The value of estimated urinary abnormalities in apparently healthy persons is open to controversy, because in many cases little that merits is likely to be found. However, we think that, if physicians would become more aware of the significance of positive findings of urinalysis, their reaction to such findings would also be altered. Major and treatable conditions

such as renal calculi, diabetes mellitus nephropathy, and urothelial tumors could be found as a part of a routine work-up. After mass screening in a medical checkup center, some subjects with positive urine hemoglobin and/or protein are referred to urologists for a second-line urological work-up. As no agreement has been reached on when to test for asymptomatic microscopic hematuria, the urologists should be guided by the results of the patient's history and physical examination. Risk factors for significant underlying disease include 1) age older than 40 years; 2) tobacco use; 3) analgesic abuse (eg, phenacetin); 4) history of pelvic irradiation; 5) cyclophosphamide; and 6) exposure to occupational toxins such as dyes, benzenes, and aromatic amines[4,14].

## SUMMARY

Dipstick urinalysis is simple and quick to perform and is among the most commonly used screening tests. In our mass screening setting by this test, the positivity of hematuria increased linearly with age in women, and that of proteinuria also increased linearly with age in men.

The true meaning of such gender- and/or age-related differences in urinary abnormalities remains to be determined.

## ACKNOWLEDGMENT

We would like to thank Mr. Keizo Fukumoto for his expert assistance.

## REFERENCES

1) Woolhandler S, Pels RJ, Bor DH, et al.: Dipstick urinalysis screening of asymptomatic adults for urinary tract disorders. I. hematuria and proteinuria. JAMA **262**: 1215–1219, 1989
2) Grossfeld GD and Carroll PR: Evaluation of asymptomatic microscopic hematuria. Urol Clin North Am **25**: 661–676, 1998
3) Grossfeld GD, Litwin MS, Wolf SJ, et al.: Evaluation of asymptomatic microscopic hematuria in adults: the American Urological Association best practice policy- Part 1: definition, detection, prevalence, and etiology. Urology **57**: 599–603, 2001
4) The Guideline of Hematuria Diagnosis by the Japanese Urological Association. Jpn J Urol **97** (Supplement), 2006
5) Mariani AJ, Luangphinith S, Loo S, et al.: Dipstick chemical urinalysis: an accurate cost-effective screening test. J Urol **132**: 64–66, 1984
6) Messing EM, Young TB, Hunt VB, et al.: The significance asymptomatic microhematuria in men 50 or more years old: findings of a heme screening study using urinary dipstics. J Urol **137**: 919–922, 1987
7) Simpson E and Thompson D: Routine urinalysis. Lancet **2**: 361–362, 1977
8) Iseki K, Iseki C, Ikemiya Y, et al.: Risk of developing renal disease in a cohort of mass screening. Kidney Int **49**: 800–805, 1996
9) Mohr DN, Offord KP, Owen RA, et al.: Asymptomatic microhematuria and urological disease: a population-based study. JAMA **256**: 224–229, 1986
10) Froom P, Gross M, Ribak J, et al.: The effect of age on the prevalence of asymptomatic microscopic hematuria. Am J Clin Pathol **86**: 656–657, 1986
11) Sakemi T, Toyoshima H and Morito F: Testosterone eliminates the attenuating effect of castration on the progressive glomerular injury in hypercholesterolemic male Imai rats. Nephron **67**: 469–476, 1994
12) Sacks SH, Aparicio SA, Bevan A, et al.: Late renal failure due to prostatic outflow obstruction: a preventable disease. BMJ **298**: 156–159, 1989
13) Shimabukuro T, Nakamura K, Uchiyama K, et al.: Renal biopsy: clinicopathological study of 126 patients. Nishinihon J Urol **67**: 273–279, 2005
14) Grossfeld GD, Litwin MS, Wolf JS, et al.: Evaluation of asymptomatic microscopic hematuria in adults: the American Urological Association best practice policy-Part II: patient evaluation, cytology, voided markers, imaging, cystoscopy, nephrology evaluation, and follow-up. Urology **57**: 604–610, 2001

(Received on January 22, 2007
Accepted on May 10, 2007)

和文抄録

# 当院健診センターを受診した男女6,651人における加齢に伴う血尿および蛋白尿陽性率の評価

島袋　智之[1]，内藤　克輔[2]
[1]宇部興産中央病院泌尿器科，[2]山口大学医学部特殊専門領域腫瘍病態学教室

健康診断のために当院健診センターを訪れ，尿潜血と蛋白尿のスクリーニング検査を受けた男女6,651人（女性：2,556人，男性：4,095人）を対象に，加齢に伴う両所見の陽性頻度の検討を行った．市販の尿試験紙法を用いて行い，採尿から試験紙法の判定までは60分以内とした．

女性の平均年齢は48.2歳（10～82歳）であり，男性は49.9歳（7～89歳）であった．女性の30.1，1.5そして0.7%，また男性の11.4，4.0そして1.5%が，それぞれ尿潜血，蛋白尿，血蛋白尿陽性所見を有していた．尿潜血陽性率は男性に比べ女性で2.6倍高く，逆に蛋白尿陽性率は男性で2.7倍高かった．尿潜血陽性率は女性においては加齢とともに増加したが（Rs＝0.943，$P$＝0.0350），蛋白尿や血蛋白尿陽性率は加齢との関連性は認められなかった（$P$＝0.8386 および $P$＝0.0639）．一方，男性においては尿潜血および血蛋白尿陽性率と加齢との間には何ら関連性が認められなかったが（$P$＝0.0845 および $P$＝0.0845），30歳以上の男性では加齢とともに蛋白尿陽性率は有意に増加した（Rs＝1.000，$P$＝0.0455）．

性や加齢に関連したこれら尿異常所見の真の意味を探るためにも，今後のさらなる検討が必要であると思われた．

（泌尿紀要 **53**：783-788，2007）