Can Hematuria Be a Predictor as well as a Symptom or Sign of Bladder Cancer?¹

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Abstract
In a case-control study of urinalysis screening in the prevention of death from bladder cancer, hematuria was present in a higher proportion of cases than controls as long as five or six years before the diagnostic evaluation that led to the diagnosis of bladder cancer. In a separate cohort study data base that permitted the follow-up of 1046 persons with a physician's diagnosis of hematuria, 11 cases of bladder cancer were diagnosed more than two (mean 7.4) years after the hematuria diagnosis (4.3 cases expected; age-sex standardized morbidity ratio, 2.5; 95% confidence interval, 1.3-4.5). Bladder cancer was ruled out initially by cystoscopy in 8 of the 11 cases. Although we cannot be certain that preexisting bladder cancer or bladder cancer risk factors did not cause the bleeding, we hypothesize that hematuria can be a predictor as well as a manifestation of bladder cancer, based on a tendency for bladder mucosa with premalignant changes to bleed. The implications for screening and clinical practice remain to be determined.

Introduction
Hematuria, either gross or microscopic, is the most common presenting symptom of bladder cancer (1). Transitional cell bladder cancers generally arise in bladder mucosa with widespread but focal premalignant changes, and occurrences and recurrences at multiple sites in the bladder are therefore common (1). It is not known whether premalignant or dysplastic bladder mucosa has a tendency to bleed, as do bladder cancers themselves, or whether a tendency to bleed might even predate the appearance of premalignant changes in bladder mucosa recognizable on pathological examination. Nor is it known how long bladder cancers, particularly the superficial types, may be present before they cause signs or symptoms that lead to their detection. In the course of a case-control study to evaluate the efficacy of standard urinalyses in preventing death due to bladder cancer (2), we noted incidentally that hematuria was associated with bladder cancer detected as long as six years later. The association of hematuria with bladder cancer diagnosed several years later was confirmed in a separate clinical data base. As a result of these observations (to be presented), we hypothesize that hematuria can be a sign of an in situ or precursor lesion as well as a manifestation of bladder cancer.

Materials and Methods
The setting for these observations is the Kaiser Permanente Medical Care Program, Northern California Region. This health maintenance organization has been providing comprehensive prepaid inpatient and outpatient care to its subscriber population, which over the past 50 years has grown from several thousand to over 2.4 million. The subscribers are ethnically and socioeconomically heterogeneous (3, 4) and comprise about 30% of inhabitants of the areas served. For the case-control study of urinalysis screening in the prevention of death from bladder cancer, described in detail elsewhere (2), we identified 290 persons with fatal bladder cancer, initially diagnosed from the 1960s through 1990, and 290 control subjects, individually matched to the cases for sex, age, and length of time in the medical care program. The control subjects were still alive when their corresponding cases died of bladder cancer. The vast majority of cancers were of the transitional cell type. The subjects' mean age was 67 years at diagnosis, and three-quarters of them were men.

Information about all urinalyses before the date of symptoms or signs that led to the workup for and discovery of bladder cancer was abstracted from the subjects' medical records. Abstractors were blinded to case-control status by masking the chart after the first evidence of bladder cancer. For the purposes of this study, hematuria was classified as microscopic if the dipstick reading was 1+ or 2+ or if microscopic examination of the spun sediment revealed 4-89 RBCs/high powered field; gross hematuria was defined as dipstick readings of 3+ or 4+ or ≥90 RBCs/high powered field (or such non-numerical readings as "many", "too numerous to count"). Another form of gross hematuria considered here was when it was reported by the patient and was the reason for performing the urinalysis, regardless of the findings. Case-control comparisons and relative risk estimation used conditional logistic regression for matched pairs, except when otherwise specified.

The second approach to this question involved a computer-stored data base of drugs dispensed and diagnoses recorded by physicians of 143,574 outpatients cared for at the Kaiser Permanente Medical Center in San Francisco. The cohort, formed by inclusion in this data base due to use of the facility's pharmacy from 1969-1973, has been carefully followed-up for the occurrence of cancer in a study primarily aimed at screening pharmaceutical drugs for possible carcinogenic effects (5). "Hematuria" was one of the computer-stored diagnoses, and it was recorded by the physicians between 1967 and 1973 in

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Results

In the case-control study, the majority of instances of hematuria fell into the microhematuria category. The association with subsequent bladder cancer was strongest in the year before signs and symptoms that led to the diagnosis of cancer and tended to become less marked the earlier we looked (Table 1). It is difficult to determine exactly the prior year when the association was present, but it seems to go back about five or six years, before which the lower confidence limit of the odds ratio drops sharply below 1.0. Adjustment for cigarette smoking and occupational bladder cancer risk, as was done in the original study of urinalysis screening (2), made little difference in the findings.

When gross hematuria on urinalysis or a patient’s report was considered together with microhematuria (Table 2), the findings were similar. Risk was quite elevated during the first year before signs or symptoms that led to diagnosis and decreased until an excess was not reliably supported by the data prior to the sixth year before signs or symptoms that led to diagnosis. Examination of either form of gross hematuria alone showed similar trends but with more irregularity because of small numbers (data not shown). When attention was restricted to subjects with at least one urinalysis during the year in question, unpaired logistic analysis, either crude or adjusted for age, sex, race, cigarette smoking, and occupational bladder cancer risk, gave similar findings for any hematuria on urinalysis (data not shown). In summary, the data from the case-control study suggest that hematuria is associated with bladder cancer diagnosed up to five or six years later.

In the pharmacy cohort, relative risk of bladder cancer as estimated by standard morbidity ratio was also elevated in patients with hematuria. Thirty-four of the 49 cases were diagnosed during the first year of follow-up; bladder cancer was probably present and the cause of the hematuria in all of these patients. Nevertheless, risk was still significantly elevated after lag periods of one and two years (Table 3).
Medical Record Review. Attention was focused on the 13 case subjects from the case-control study of fatal bladder cancer who had hematuria 5–6 years before the symptoms that led to the diagnosis of this cancer, the earliest year in which the association was still substantial (Table 2). Two had transient hematuria associated with urinary tract infection, and 11 had microhematuria, which was transient in all but 1 patient. In three of these patients, the bladder was visualized by cystoscopy well before the cancer symptoms and cancer was not found.

Of the 11 case subjects in the pharmacy cohort in whom bladder cancer was detected at least 2 years after a diagnosis of hematuria, 10 had gross hematuria and 1 had transient microhematuria. Eight of these patients had had cystoscopy, with no bladder cancer apparent, well before the cancer was diagnosed. Of the other three, one patient was noncompliant and two had other conditions that were believed to be responsible for the hematuria. The bladder cancers were diagnosed 3.5–14.5 years after the hematuria was recorded; the mean interval was 7.4 years.

It should be noted that not all of these case subjects had hematuria clearly connected with their subsequent bladder cancer. Because 6 controls had hematuria 5–6 years before the cases’ symptoms leading to the diagnosis of cancer (Table 2), about 7 of the 13 cases had the hematuria linked to subsequent bladder cancer. The same can be said of about 7 of the 11 cases in the pharmacy cohort after a 2-year lag because 4.3 cases were expected in the absence of hematuria (Table 3).

Discussion
An association between hematuria and bladder cancer diagnosed a few to several years later was discovered incidentally in a case-control study, which focused on fatal cases because it was primarily a study of the efficacy of urinalysis screening in preventing death from bladder cancer. The confirmatory study in the pharmacy cohort included all incident cases, both fatal and nonfatal, indicating that our findings are generalizable beyond only fatal cases.

There are three plausible explanations for this association: (a) first, bladder cancer may have been present and causing the hematuria but was not detected; (b) second, there may be premalignant changes in the bladder mucosa that both increase the likelihood of bleeding and lead to the occurrence of bladder cancer years later; and (c) third, persons at high risk of bladder cancer may have a heightened tendency to bleed into the urine even before premalignant changes in the bladder mucosa occur.

The possibility that bladder cancer caused the initial hematuria but was not recognized at the time is more likely for the cases in the case-control study whose records were reviewed because only 3 of 13 had an informative cystoscopy well before the bladder cancer was detected. However, a large majority of the pharmacy cohort cases (8 of 11) did have bladder cancer apparently ruled out initially by cystoscopy. Also, the hematuria-to-bladder-cancer intervals considered here are long, and it seems unlikely that it would have taken a bleeding cancer several years to become clinically evident if it had been missed initially. Nevertheless, cystoscopy may not discover as many as 9% of bladder cancers (6, 7), so failure of initial detection may account, at least in part, for our findings. Urinary cytology was not performed; whether this would have allowed for earlier detection of bladder cancer is unknown.

The explanation that bladder mucosa with premalignant changes has a tendency to bleed bears serious consideration. We were not able to find direct support for this hypothesis in the literature, but we (E. V. C.) have observed that areas of bladder mucosa that prove to show dysplastic changes or cancer in situ on biopsy are often red in appearance, suggesting hyperemia. Hyperemic mucosa may well have a greater tendency to bleed than normal mucosa. Furthermore, precursor lesions or frank carcinoma in situ are characterized by a disorderly pattern of epithelial growth and absence of the normal superficial epithelial umbrella cells (8). They are likely to have a greater tendency to bleed than normal mucosa.

To evaluate whether persons at high risk of developing bladder cancer are apt to experience hematuria before premalignant changes occur in bladder mucosa, it would be useful to determine whether known risk factors for this cancer, such as cigarette smoking and industrial exposures to certain dyes and other carcinogenic chemicals, can cause hematuria. We found no published evidence for this hypothesis. The fact that controlling for cigarette smoking and occupational bladder cancer risk made little difference in the results of the case-control study makes this explanation unlikely. Analgesic abuse, another potential cause of urothelial cancer, was not evident in these subjects (2).

Of the three proposed explanations, a bleeding tendency of bladder mucosa with premalignant changes seems the most likely, but further confirmation is needed.

If persons with unexplained hematuria are indeed at increased risk of bladder cancer, our case reviews suggest that this is true for both gross and microscopic hematuria. This would indicate that unexplained hematuria of any intensity should increase one’s index of suspicion that bladder cancer, if not already present, may develop in the future. It remains to be determined what, if any, action should be taken as a result of this heightened suspicion. The potential yield of increased screening, diagnostic, and follow-up procedures must be weighed against their immediate and secondary complications and costs. Because transient asymptomatic microhematuria occurs so commonly without obvious serious pathology needing prompt treatment (9–11), and without cancer becoming evident for many years thereafter (12), it is likely to merit less intense pursuit than unexplained gross hematuria.

In summary, the hypothesis that we propose here is that hematuria can be a predictor as well as a symptom or sign of bladder cancer, most probably due to premalignant changes in the bladder mucosa.

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References


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