17. Screening for Bladder Cancer

RECOMMENDATION

Routine screening for bladder cancer with urine dipstick, microscopic urinalysis, or urine cytology is not recommended in asymptomatic persons. All patients who smoke tobacco should be routinely counseled to quit smoking (see Chapter 54).

Burden of Suffering

Bladder cancer is an important cause of morbidity and mortality in the U.S., primarily in older men. Over 50,000 new cases and over 11,000 deaths due to bladder cancer are predicted to occur in 1995 in the U.S.[1] Risk rises steeply with age; over half of all deaths from bladder cancer occur after age 70. The incidence of bladder cancer is 3–4 times higher in men than women, and roughly twice as high in white men compared to black men.[2,3] Among white men, the annual incidence of bladder cancer after age 65 is approximately 2/1,000 persons (vs. 0.1/1,000 under 65), and the lifetime probability of developing cancer is over 3%.[3] The probability of dying from bladder cancer is much smaller, however—less than 1%. Cigarette smoking markedly increases the risk for bladder cancer (relative risk among smokers vs. nonsmokers = 1.5–7);[4,5] nearly half of all new cases of bladder cancer occur in current or former smokers.[2] Occupational exposure to chemicals used in dye, leather, and tire and rubber industries has also been associated with increased risks of bladder cancer.[4] Despite initial reports, positive associations between bladder cancer and consumption of coffee or artificial sweeteners have not been confirmed.[2,6,7]

Accuracy of Screening Tests

Early asymptomatic bladder cancer may be associated with occult bleeding (microscopic hematuria) or the presence of dysplastic cells in the urine. The definition of significant hematuria varies, but more than 3–5 red blood cells (RBCs) per high-powered field in microscopic analysis of the urine sediment is usually considered abnormal.[8] Urine dipsticks, which detect peroxidase activity of hemoglobin, provide a quick, inexpensive, and sensitive test for hematuria, and have largely supplanted microscopic urinalysis for screening in asymptomatic patients. Depending on the reference standard used (>2 or >5 RBCs per high-powered field on microscopy), dipstick urinalysis has a sensitivity of 91–100% and a specificity of 65–99% for de-

tecting microscopic hematuria.[9–16] Dipsticks facilitate testing of serial urine specimens at home, which increases the detection of intermittent hematuria. False-positive dipstick results may be produced by myoglobin in the urine, and false-negative results may result from high concentrations of ascorbic acid, or from prolonged exposure of dipsticks to air.[8]

Although dipsticks are reasonably accurate for detecting hematuria, microscopic hematuria is not specific for bladder cancer or other urologic cancers. Of the various other causes of microscopic hematuria in asymptomatic patients, most are either benign (e.g., benign prostatic hypertrophy (BPH), exercise, renal cysts, urethral trauma, menstrual bleeding) or of questionable importance (bladder stones, dysplasia, asymptomatic infection). In three separate studies, 46–55% of men with asymptomatic hematuria had no identifiable source of bleeding.[17–19]

Two large outpatient studies have used urine dipsticks to screen for hematuria in asymptomatic populations at increased risk of bladder cancer. In a study by Messing, older men (mean age 65) screened their urine daily for 14 days. Of 1,340 men completing screening, 21% had at least one positive screen and 16 (1.2%) had urologic cancers (9 bladder, 1 renal, and 6 prostate).[18] Britton recruited 3,152 male outpatients over 60 years old to test their urine 10 times (daily or weekly). At least one screen was positive in 20% of men (12% on initial screen), and 22 (0.5%) had cancer (17 bladder and 5 prostate).[19] Among men undergoing full evaluation for hematuria, the positive predictive values (PPV) of serial dipstick screening for malignancy in these two studies were 8% and 6%, respectively; one third of men with hematuria refused or had an incomplete workup in each study. Similar results have been reported in other populations: among 272 Japanese men with 5 or more RBCs on urinalysis, 6% had urologic cancers.[17] Hematuria has a higher PPV (26–33%) if other urologic disorders are included as useful outcomes of screening,[18,20] but the benefit of early detection of many of these conditions (bladder stones, mild obstruction, urinary tract infection) remains unproven in asymptomatic individuals (also see Chapter 31).

The yield of onetime screening for bladder cancer in the general outpatient population appears to be much lower. In a retrospective review of over 20,000 men over 35 and women over 55 receiving a personal health appraisal, dipstick screening detected only three cases of cancer (one bladder, two prostate).[21] Prevalence of positive dipstick results ranged from 3–9% over a 7-year period. In a second study of almost 2,700 outpatients, 13% of screened men and women had hematuria (at least one RBC on urine sediment), but only 2% of those with microscopic hematuria had serious urologic disease.[22,23] In each of these studies, only 0.5% of all patients (3–4% of men over age 55) with asymptomatic hematuria were diagnosed with urologic cancers within 3 years of a positive screen.

Urine cytology is more specific but less sensitive than microscopic hematuria as a screen for early bladder cancer. Because cytology is technically difficult and significantly more expensive than dipstick urinalysis, its use as an initial screening test has been limited to high-risk occupational screening programs. Specificity for cytology has been estimated to be as high as 95%,[24] and sequential screening combining urine dipstick and urine cytology may be able to reduce the false-positive rate of screening while maintaining sensitivity for clinically important cancers. Among men with dipstick hematuria in one screening study, urine cytology detected 10 of 17 patients with bladder cancer with a specificity of 96%; 6 of the 7 cases missed were well-differentiated, superficial lesions with a good prognosis.[19] Rapid tests based on other tumor markers are under investigation.[25]

Effectiveness of Early Detection

Survival in patients with bladder cancer is strongly associated with stage at diagnosis. Although most cancers are superficial at time of diagnosis, currently 10–20% of all cases of bladder cancer have invaded the muscular wall of the bladder when first diagnosed, with a much worse prognosis. Five-year survival for patients with superficial disease is over 90%, but falls to less than 50% with invasive disease.[1] The rationale for screening is that detecting and treating early asymptomatic bladder cancers may prevent progression to invasive disease, or allow for more effective treatment of noninvasive tumors, which have a high rate of recurrence. Many cases detected on screening, however, are low-grade transitional cell cancers with low propensity for invasion; in contrast, since aggressive cancers may invade early, periodic screening may have a limited potential for detecting lethal bladder cancers at an early, treatable stage.[26]

In the prospective screening studies cited above, all 26 cases of bladder cancer detected by screening were early tumors confined to superficial areas of the bladder (Stage T0 or T1).[18,19] Compared to outcomes of cancers developing in the general population, cases detected by screening appeared to be less likely to progress over 3 years[27] or lead to death within 2 years.[28] Because of lead-time and length biases (see Chapter ii, Methodology), however, comparing case-survival is not sufficient to establish a benefit of screening, without information on rates of cancer and death in a comparable unscreened population. The incidence of invasive and fatal bladder cancer among screened men is very low, and it is also quite low in the general population of older men (<1/1,000 per year). Larger studies, with a comparable unscreened group and longer follow-up, are needed to determine whether screening improves the outcome of bladder cancer in high-risk populations. Despite early detection and treatment, 10 of 16 cancers detected by screening recurred within 3 years in one study.[27]

Recommendations of Other Groups

No major organization recommends screening for bladder cancer in asymptomatic adults. The Canadian Task Force on the Periodic Health Examination recommends against routine screening in asymptomatic individuals and concludes that there is insufficient evidence for or against screening in specific high risk groups.[29] The American Cancer Society has not issued any specific guidelines on screening for bladder cancer.

Discussion

Dipstick and microscopic urinalysis are simple and sensitive tests for detecting hematuria from early tumors, but they are not sufficiently specific to be practical for screening for bladder cancer in the general population. Even among older high-risk populations, the predictive value of a positive screening test is low (5–8%). As a result, many persons without cancer will require diagnostic workups for false-positive test results and will be subjected to the costs, discomforts, and risks of cystoscopy and intravenous pyelography. More important, there is no proof that early detection significantly improves the prognosis for the small minority of patients found to have urologic malignancies. Most of the bladder cancers detected have a good prognosis in the absence of screening: 5-year survival for all bladder cancer is currently close to 80%.[1] Due to the frequent multifocal nature of bladder cancer, recurrences are common despite early detection and treatment. Conversely, the most lethal tumors become invasive early in the course of disease, and the potential to detect them at an earlier stage may be limited. Only a prospective study that includes an unscreened comparison group can determine whether screening is effective in reducing morbidity or mortality from bladder cancer (or other urologic cancers), and whether the benefits are sufficient to justify the costs and risks of screening and early treatment. In the absence of such evidence, routine screening cannot be recommended, due to the high rate of false-positive results, and the possibility of harm to asymptomatic patients, few of whom have cancer. Primary prevention may offer a safer and more effective strategy than screening for reducing mortality from urologic cancer, since smoking accounts for nearly half of all deaths from cancers of the bladder and kidney.[2]

CLINICAL INTERVENTION

Routine screening for bladder cancer with microscopic urinalysis, urine dipstick, or urine cytology is not recommended in asymptomatic persons (“D” recommendation). Persons working in high-risk professions (e.g., dye or rubber industries) may be eligible for screening at the worksite, although the benefit of this has not been determined. Men and women who smoke cigarettes should be advised that smoking significantly increases the

risk for bladder cancer, and all smokers should be routinely counseled to quit smoking (see Chapter 54).

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