Screening for Bladder Cancer: A Brief Evidence Update for the U.S. Preventive Services Task Force

Epidemiology

The incidence of bladder cancer in the United States in the year 2000 was approximately 21 per 100,000 persons.[3] The American Cancer Society estimates that 60,240 new cases of bladder cancer will be diagnosed in the United States during 2004 (about 44,640 men and 15,600 women), and about 12,710 people will die of the disease (about 8,780 men and 3,930 women).[4] Bladder cancer occurs primarily in men older than 60 and roughly twice as frequently in white men as in black men.[3] Men are 2.5 times more likely to be diagnosed with bladder cancer than women; age-adjusted mortality rates from bladder cancer are similarly higher for men than for women.

Cigarette smoking is the greatest environmental risk factor for bladder cancer. Cigarette smokers are 4 to 7 times more likely to develop bladder cancer than nonsmokers.[5] Occupational exposures to chemicals (aromatic amines) used in dry cleaning facilities and the production of dyes, paper, rope and twine, and apparel have been associated with increased risk for bladder cancer. Other industrial exposures implicated as risk factors for developing bladder cancer include combustion gases and soot from coal, chlorinated aliphatic hydrocarbons, and chlorination by-products in heated water.[5]

Bladder cancer is a heterogeneous condition. More than 50% of bladder cancers are low-grade and superficial at diagnosis. Although these cancers recur frequently after treatment, they rarely invade muscle and rarely cause clinically significant morbidity or mortality.[6,7,8] The natural history of untreated bladder cancer is unclear; it is estimated that about 50% of high-grade superficial bladder cancers eventually invade muscle.[9] People with high-grade cancer that has invaded muscle by the time of detection have a poor prognosis. The effectiveness of treatment for those with high-grade bladder cancer is uncertain.[10] The variability in the natural history of bladder cancer and the low prevalence of asymptomatic bladder cancer in the general population present problems in evaluating the effectiveness of screening for this disease.

Methodology

We employed a general search strategy, limited to the English language and the years 1994 to 2002, to search MEDLINE using *bladder neoplasms* as an "exploded" MeSH term. We combined *bladder neoplasms* separately with *mass screening,* which yielded 28 citations, and with *meta-analysis,* which yielded 23 citations. We then combined *bladder neoplasms* with *therapeutics/treatment* (1,984 citations) and combined those results with *outcome,*

Systematic Evidence Reviews serve as the basis for U.S. Preventive Services Task Force (USPSTF) recommendations on clinical prevention topics. The USPSTF tailors the scope of these reviews to each topic. The Task Force determined that a brief evidence update was needed to assist in updating its 1996 recommendations on screening for bladder cancer.[1]

To assist the USPSTF, the RTI International-University of North Carolina Evidence-based Practice Center, under contract to the Agency for Healthcare Research and Quality (AHRQ), performed a targeted review of the literature published on this topic between 1994 and 2002. This brief evidence update on screening for bladder cancer and the updated recommendation statement[2] are available through the AHRQ Web site (www.preventiveservices.ahrq.gov) and in print through subscription to the *Guide to Clinical Preventive Services, Third Edition: Periodic Updates.* The subscription costs $60 and can be ordered through the AHRQ Publications Clearinghouse (call 1-800-358-9295, or e-mail ahrqpubs@ahrq.gov). The recommendation is also posted on the Web site of the National Guideline Clearinghouse™ (www.guideline.gov).

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which yielded 189 citations. Finally, we combined *bladder neoplasms* with *randomized controlled trial* and then combined those results with *single-blind or double-blind method,* which yielded another 189 citations.

We performed a separate search for 2 new bladder tumor markers, NMP22 (nuclear matrix protein 22) and BTA (bladder tumor antigen). We used *tumor markers, sensitivity and specificity,* and *antigens, neoplasm* as "exploded" MeSH terms and combined them with NMP22, yielding 22 citations.

Two reviewers independently analyzed all citations and culled abstracts that fit eligibility criteria for assessment. Two independent reviewers then obtained full text articles of potentially suitable abstracts and excluded those not meeting eligibility criteria.

Key Questions and Results

1. Is there direct evidence that screening for bladder cancer reduces morbidity or mortality?

We found no high-quality direct evidence addressing the effectiveness of screening for bladder cancer on morbidity or mortality from that disease.

Two cohort studies addressed this question but provided insufficient evidence to judge the effectiveness of screening. Messing et al[11] investigated the ability of repetitive hematuria home screening with a chemical reagent strip to effect earlier detection and reduce bladder cancer mortality. The investigators found that only 1 of 21 (4.8%) men from primary care clinics whose bladder cancers were detected by hematuria screening had muscle invasive cancer (stage T2 or greater) compared with 122 of 511 (23.9%) men with bladder cancer as reported to the state cancer registry. In addition, 16.4% of the patients from the cancer registry with bladder cancer died of bladder cancer within 2 years, while none of the study patients whose cancer was detected through screening died during that time ($P = 0.025$). These differences, however, could have been caused by several factors other than screening: the small number of bladder cancers in the screened group, differences between the men in the comparison groups, and lead-time bias or length-biased sampling.

In the second cohort study, Mayfield et al[12] reported the outcomes of 16 men whose bladder cancers were detected in a community screening project. Initially, all these cancers were superficial and were treated routinely. Among 7 men with well-differentiated tumors, none progressed to muscle-invasive disease after 7 years of follow-up. Among the 9 men with higher grade cancer at diagnosis, 3 died of bladder cancer within 7 years, and 2 others progressed to muscle-invasive disease. Conclusions from this study are limited by the small number of cancers and the lack of a control group to provide information about bladder cancer outcomes in the absence of screening.

2. What are the accuracy and reliability of feasible screening tests for bladder cancer?

Several studies examined the accuracy of hematuria, bladder tumor antigen, NMP22 urinary enzyme immunoassay, and urine cytology.[13–17] All had important flaws, especially involving screening patients from urology clinics (as opposed to average risk populations from primary care clinics) or not applying "gold standard" tests (cystoscopy with or without biopsy) to those who screened negative for bladder cancer. As a result, these studies do not provide high-quality evidence about the accuracy of screening tests in the general primary care population.[18]

3. Does treatment of early-stage bladder cancer reduce morbidity and mortality from this disease?

We found no high-quality studies that compared health outcomes in treated and untreated groups for the early-stage bladder cancers that would be detected by screening. Since these cancers may or

may not progress to clinically significant morbidity or mortality, such direct comparisons of treated and untreated groups are necessary.

Summary

We found no high-quality direct evidence addressing the effectiveness of screening for bladder cancer on morbidity or mortality from that disease. We found no studies on the accuracy and reliability of screening tests for bladder cancer that allow us to accurately determine the sensitivity or specificity of screening in the general primary care population. We found no high-quality trials that compared health outcomes in treated and untreated groups with the type of bladder cancer that would be detected by screening.

Recommendations of Others

No major organization recommends screening for bladder cancer in asymptomatic adults. The Canadian Task Force on Preventive Health Care recommends against routine screening in asymptomatic individuals and concludes that there is insufficient evidence for or against screening in specific high-risk groups.[19] The American Academy of Family Physicians recommends against screening for bladder cancer in asymptomatic persons using microscopic or dipstick urinalysis.[20]

References

1. U.S. Preventive Services Task Force. *Guide to Clinical Preventive Services.* 2nd ed. Washington, DC: Office of Disease Prevention and Health Promotion; 1996.
2. U.S. Preventive Services Task Force. Screening for bladder cancer in adults: recommendation statement. June 2004. Agency for Healthcare Research and Quality, Rockville, MD. Available at www.preventiveservices.ahrq.gov.
3. U.S. Cancer Statistics Working Group. *United States Cancer Statistics: 2000 Incidence.* Atlanta, GA: Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2003. Available at: http://www.cdc.gov/cancer/npcr/uscs/2000/index.htm. Accessed February 12, 2004.
4. American Cancer Society. *Detailed Guide: Bladder Cancer: What Are the Key Statistics for Bladder Cancer?* Atlanta, GA: American Cancer Society. 2004. Available at: http://www.cancer.org/docroot/CRI/CRI_2_3x.asp?dt=44. Accessed February 12, 2004.
5. National Cancer Institute. Screening for bladder cancer (PDQ®): Health Professional Version; 2004. Available at: http://cancer.gov/cancerinfo/pdq/screening/bladder/healthprofessional/. Accessed February 12, 2004.
6. Goldstein MM, Messing EM. Prostate and bladder cancer screening. *J Am Coll Surg.* 1998;186:63–74.
7. Prout GR Jr, Barton BA, Griffin PP, Friedell GH. Treated history of noninvasive grade 1 transitional cell carcinoma. *J Urol.* 1992;148(5):1413–1419.
8. Kaye KW, Lange PH. Mode of presentation of invasive bladder cancer: reassessment of the problem. *J Urol.* 1982;128(1):31–33.
9. Heney NM, Ahmed S, Flanagan MJ, et al. Superficial bladder cancer: progression and recurrence. *J Urol.* 1983;130:1083–1086.
10. van der Meijden APM. Bladder cancer: fortnightly review. *BMJ.* 1998;317:1366–1369.
11. Messing EM, Young TB, Hunt VB, et al. Comparison of bladder cancer outcome in men undergoing hematuria home screening versus those with standard clinical presentations. *Urology.* 1995; 45:387–396; discussion 396–397.
12. Mayfield MP, Whelan P. Bladder tumours detected on screening: results at 7 years. *Br J Urol.* 1998; 82:825–828.
13. Raitanen MP, Tammela TL. Specificity of human complement factor H-related protein test (Bard BTA stat test). *Scand J Urol Nephrol.* 1999;33:234–236.
14. Zippe C, Pandrangi L, Agarwal A. NMP22 is a sensitive, cost-effective test in patients at risk for bladder cancer. *J Urol.* 1999;161:62–65.

15. Messing EM, Young TB, Hunt VB, et al. Hematuria home screening: repeat testing results. *J Urol.* 1995; 154:57–61.

16. Ponsky LE, Sharma S, Pandrangi L, et al. Screening and monitoring for bladder cancer: refining the use of NMP22. *J Urol.* 2001;166:75–78.

17. Miyanaga N, Akaza H, Tsukamoto T, et al. Urinary nuclear matrix protein 22 as a new marker for the screening of urothelial cancer in patients with microscopic hematuria. *Int J Urol.* 1999;6:173–177.

18. Whiting P, Rutjes AWS, Reitsma JB, Glas AS, Bossuyt PMM, Kleijnen J. Sources of variation and bias in studies of diagnostic accuracy. *Ann Intern Med.* 2004;140:189–202.

19. Canadian Task Force on the Periodic Health Examination. *Canadian Guide to Clinical Preventive Health Care*. Ottawa: Canada Communication Group; 1994. Available at: http://www.ctfphc.org/. Accessed March 10, 2004.

20. American Academy of Family Physicians. *AAFP Summary of Policy Recommendations for Periodic Health Examination.* Available at: http://www.aafp.org. Accessed March 10, 2004.

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