Annals of Internal Medicine | Clinical Guideline

Screening Adults for Bladder Cancer: A Review of the Evidence for the U.S. Preventive Services Task Force

Roger Chou, MD, and Tracy Dana, MLS

Background: Bladder cancer is 1 of the 10 most frequently diagnosed types of cancer. Screening could identify high-grade bladder cancer at earlier stages, when it may be more easily and effectively treated.

Purpose: To update the 2004 U.S. Preventive Services Task Force evidence review on screening for bladder cancer in adults in primary care settings.

Data Sources: MEDLINE (2002 to December 2009), the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials (through the fourth quarter of 2009), and the CancerLit subsection of PubMed (through March 2010) were searched for studies published in English.

Study Selection: Randomized trials and controlled observational studies that directly evaluated screening for bladder cancer in adults, studies on the diagnostic accuracy of screening tests for bladder cancer, and randomized trials and controlled observational studies on clinical outcomes associated with treatment compared with no treatment of screen-detected or superficial bladder cancer.

Data Extraction: Details were abstracted about the patient sample, study design, data analysis, follow-up, and results. Quality was assessed by using methods developed by the U.S. Preventive Services Task Force.

Data Synthesis: No randomized trials or high-quality controlled observational studies evaluated clinical outcomes associated with screening compared with no screening or treatment of screen-detected bladder cancer compared with no treatment. No study evaluated the sensitivity or specificity of tests for hematuria, urinary cytology, or other urinary biomarkers for bladder cancer in asymptomatic persons without a history of bladder cancer. The positive predictive value of screening is less than 10% in asymptomatic persons, including higher-risk populations. No study evaluated harms associated with treatment of screen-detected bladder cancer compared with no treatment.

Limitation: High-quality evidence was not available for any of the key questions.

Conclusion: Additional research is needed to determine whether screening of adults for bladder cancer leads to better outcomes compared with no screening.

Primary Funding Source: Agency for Healthcare Research and Quality.

Ann Intern Med. 2010;153:461-468. www.annals.org
For author affiliations, see end of text.

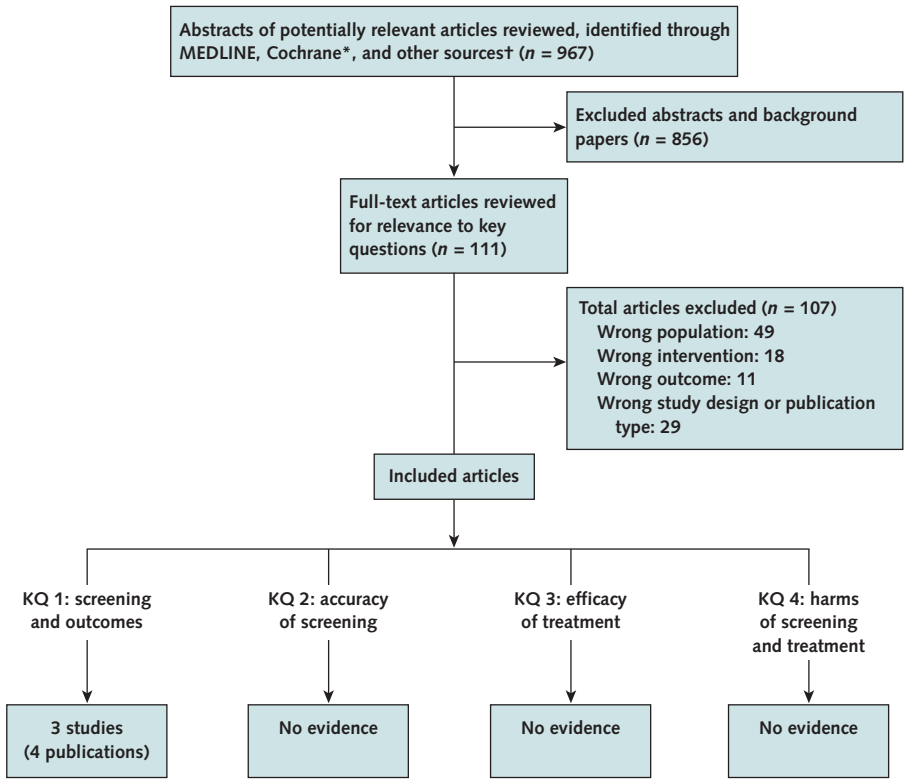
The incidence of bladder cancer in the United States in 2005 was approximately 21 per 100 000 persons, or 0.02% (1). The American Cancer Society estimates that 70 980 new cases of bladder cancer will be diagnosed in the United States during 2009 (about 52 810 men and 18 170 women), and about 14 330 persons will die of the disease (about 10 180 men and 4150 women) (2). Bladder cancer ranks as the fourth most commonly diagnosed cancer in U.S. men and the ninth most commonly diagnosed cancer in women. Risk factors for bladder cancer include older age, male sex, white race, smoking, occupational exposures, infections caused by certain bladder parasites, and a family or personal history of bladder cancer (1, 3–6).

Bladder cancer is a heterogeneous condition. In the United States, more than 90% of bladder cancer is transitional-cell carcinoma, 5% is squamous-cell carcinoma, and less than 2% is adenocarcinoma (7–9). Bladder cancer tumor staging is based on the extent of penetration into the bladder wall and adjacent structures (10, 11). Superficial bladder cancer, or cancer that has not invaded the bladder smooth muscle, includes stages Ta (noninvasive papillary carcinoma), Tis (carcinoma in situ), and T1 (tumor invades subepithelial connective tissue) tumors. Stage 2 tumors and higher are muscle-invasive. Approximately 75% of newly diagnosed transitional-cell carcinomas present as superficial tumors, and 25% present as invasive tumors (12). The main treatment of superficial bladder cancer is local (bladder-sparing) resection (transurethral resection of bladder tumor), often with adjuvant radiation therapy, intravesical chemotherapy, immunotherapy, or photodynamic therapy (13). As many as 50% to 70% of superficial tumors recur after initial treatment, and 10% to 20% progress to invasive tumor (7). The likelihood of progression from superficial to invasive cancer is affected by the presence of more poorly differentiated cells and other histopathologic features; the number, size, and appearance of lesions; the response to initial treatment; and other factors (14). Once bladder cancer invades muscle, it can quickly progress and metastasize and is associated with a poor prognosis. The main treatment of surgically resectable

See also:

Web-Only
Appendix Tables
Appendix Figure
CME quiz
Conversion of graphics into slides

Figure. **Summary of evidence search and selection.**



KQ = key question.
* Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
† Other sources include reference lists.

invasive bladder cancer is radical cystectomy, often with adjuvant or neoadjuvant systemic chemotherapy.

Screening could identify high-grade superficial bladder cancer at earlier asymptomatic stages, when there is a greater chance of cure with bladder-sparing therapies (15). Screening tests that might be feasible for primary care include tests for hematuria, urinary cytology, and other urinary biomarkers. The U.S Preventive Services Task Force (USPSTF) last reviewed the evidence on bladder cancer screening in 2004 but found insufficient evidence to guide a recommendation (16).

The USPSTF commissioned an update of the evidence review in 2009 in order to update its recommendation. Bladder cancer remains an important public health problem, with no improvements in incidence or associated mortality since 1975 (17). There is important uncertainty about bladder cancer screening, particularly in higher-risk patients. In addition, since the last USPSTF review, research on urinary biomarkers for diagnosis of bladder cancer has accumulated substantially. The purpose of this report is to systematically evaluate the current evidence on screening for bladder cancer. The **Appendix Figure** (available at www.annals.org) shows the analytic framework and key questions used to guide our review.

Methods

Data Sources

We searched the MEDLINE database from 2002 to December 2009, the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials through the fourth quarter of 2009, and the CancerLit subsection of PubMed through March 2010 to identify relevant articles (see **Appendix Table 1**, available at www.annals.org, for the full search strategy). We identified additional studies from reference lists of relevant articles, including the previous USPSTF review.

Study Selection

The **Figure** shows the flow of studies from initial identification of titles and abstracts to final inclusion or exclusion. We selected studies on the basis of predefined inclusion and exclusion criteria (**Appendix Table 2**, available at www.annals.org). Two reviewers evaluated each study at the title or abstract and full-text article stages to determine eligibility for inclusion.

The target population was asymptomatic persons older than 50 years. We focused on studies done in primary care settings but also included studies conducted in occupa-

tional settings. Studies that enrolled patients with recurrent bladder cancer were excluded unless the proportion of such patients was less than 10%. We also excluded studies that enrolled patients with gross hematuria and dysuria or other signs and symptoms associated with bladder cancer.

We included randomized, controlled trials (RCTs) and controlled observational studies (cohort and case-control) that directly assessed the effects of bladder cancer screening compared with no screening on morbidity, mortality, or harms. We also included studies that evaluated the diagnostic accuracy of urinalysis for hematuria, urinary cytology, and other urinary biomarkers compared with the results of cystoscopy. Studies of diagnostic accuracy that did not perform the reference standard in patients with negative screening results were excluded because sensitivity and specificity cannot be calculated. For treatment, we focused on RCTs and controlled observational studies comparing benefits and harms of transurethral resection of bladder tumor, intravesical therapy, or both compared with no treatment of screen-detected or superficial bladder cancer. We restricted our review to studies published in English.

Data Abstraction and Quality Assessment

We abstracted details on patient population, study design, data analysis, follow-up, and results. One author abstracted data, and another author checked the abstracted data. We used predefined criteria developed by the USPSTF to assess the risk for bias (quality) of studies (**Appendix Table 3**, available at www.annals.org) (18, 19). For randomized trials, we assessed methods of randomization, allocation concealment, blinding, loss to follow-up, and use of intention-to-treat analysis. Two authors independently rated the internal validity of each study as good, fair, or poor on the basis of the number and seriousness of methodological shortcomings. For all studies, we evaluated applicability to populations likely to be encountered in primary care settings. The potential applicability of studies to primary care was assessed on the basis of whether patients were recruited from primary care or community settings, the proportion of patients with signs or symptoms suggesting bladder cancer, occupational exposures, the stage of bladder cancer, and the proportion of patients with a previous bladder cancer diagnosis. We resolved discrepancies in quality ratings by discussion and consensus.

Data Synthesis and Analysis

When data were available from diagnostic accuracy studies, we used the diagti procedure in Stata, version 10 (StataCorp, College Station, Texas), to calculate sensitivities, specificities, and likelihood ratios.

We assessed the overall strength of the body of evidence for each key question (good, fair, or poor) by using methods developed by the USPSTF, on the basis of the number, quality, and size of studies; consistency of results among studies; and directness of evidence (18). Because few studies met inclusion criteria, we did not quantitatively pool results.

Role of the Funding Source

The Agency for Healthcare Research and Quality funded this work under a contract to support the work of the USPSTF. Agency staff and USPSTF members participated in development of the initial scope of this work and reviewed draft manuscripts. A draft version was distributed to content experts for review. Agency approval was required before this manuscript could be submitted for publication, but the authors are solely responsible for the content and the decision to submit it for publication.

Results

Is There Direct Evidence That Screening for Bladder Cancer Reduces Morbidity or Mortality? (Key Question 1)

We identified no RCTs of screening for bladder cancer. One older, prospective study (20) was included in the previous USPSTF report, with results reported for up to 8.5 years of follow-up (16) (**Table 1**). For this update, we included results through 14 years of follow-up. The study evaluated screening in 1575 community-dwelling men 50 years or older, with a comparison group consisting of 511 patients who recently received a diagnosis of bladder cancer entered in a statewide registry. Screening was based on repeated urine self-testing at home for up to 1 year. A total of 16% (258 of 1575) of screened men had hematuria, and 1.3% (21 of 1575) received a diagnosis of bladder cancer, including 1 case of muscle-invasive cancer (0.06%). The study found no difference in the proportion of low-grade, superficial bladder cancer or invasive bladder cancer at the time of diagnosis in the screen-detected and cancer-registry groups, but the proportion of high-grade, superficial bladder cancer was higher in the screened group (43% vs. 19%; RR, 2.2 [95% CI, 1.3 to 3.7]). After 14 years of follow-up, the risk for bladder-cancer–related death was lower in the screened group than in the cancer-registry patients (0% [0 of 21] vs. 20% [104 of 509]; $P = 0.01$), primarily because of the decreased risk in patients with high-grade or invasive cancer (0% [0 of 10] vs. 38% [77 of 200]; $P = 0.01$) (22). Largely due to the effects on bladder-cancer–related death, the risk for all-cause mortality was also lower in the screened group (43% [9 of 21] vs. 74% [377 of 509]; RR, 0.58 [CI, 0.35 to 0.95]).

This study was rated poor-quality because it did not assemble an inception cohort of similar unscreened persons. Results are highly susceptible to confounding, lead-time bias, length-time bias, sparse data (due to no deaths in the screened group), and other factors. No attempt was made to adjust or control for potential confounders. The study reported bladder cancer rates among the cohort of men invited to enroll in the screening study but who declined (based on cases reported to the statewide registry). Rates of new bladder cancer were identical among screened

Table 1. **Screening Studies**

Study, Year (Reference)	Population	Study Design	Screening Test	Sample Size	Results	Quality Score
Friedman et al, 1995 (21)	Case patients: fatal bladder cancer among Kaiser Permanente subscribers Control participants: living; a member of Kaiser Permanente; matched on age, sex, and date of joining program	Case–control study	Urinalysis	290 case patients and 290 control participants	Bladder cancer death vs. living matched control participants: Screening urinalysis within the 5 y before symptoms or findings leading to the cancer diagnosis (adjusted for smoking and occupational bladder cancer risk): OR, 0.60 (95% CI, 0.41–0.87) Any urinalysis within the 5 y before symptoms or findings leading to the cancer diagnosis (adjusted for smoking and occupational bladder cancer risk): OR, 0.94 (CI, 0.61–1.46)	Poor; unable to accurately ascertain reason for urinalyses or presence of symptoms
Messing et al, 1995 (20) and 2006 (22)	Asymptomatic men aged >50 y from primary care settings (screening population) and bladder cancer cases reported to a statewide registry in the United States	Prospective cohort of screened persons compared with cases reported to a statewide registry	Periodic home urinalysis for hematuria	1575 in screening cohort (1940 declined to participate); 511 cases reported to cancer registry	Rate of positive screenings: 16% (258 of 1574) Positive predictive value: 8% (21 of 258) Screened patients vs. registry cases: Low-grade superficial bladder cancer at diagnosis: 52% (11 of 21) vs. 57% (290 of 511); RR, 0.92 (CI, 0.61–1.4) High-grade superficial bladder cancer at diagnosis: 43% (9 of 21) vs. 19% (99 of 511); RR, 2.2 (CI, 1.3–3.7) Muscle-invasive or higher-stage bladder cancer at diagnosis: 4.8% (1 of 21) vs. 24% (122 of 511); RR, 0.20 (CI, 0.03–1.4) Bladder cancer death at 14 y: 0% (0 of 21) vs. 20% (104 of 509); $P = 0.01$ Overall mortality at 14 y: 43% (9 of 21) vs. 54% (273 of 509); RR, 0.80 (CI, 0.48–1.32) Screened patients vs. unscreened patients: Bladder cancer diagnosis: 1.3% (21 of 1574) vs. 1.2% (23 of 1940)	Poor; no inception cohort of similar unscreened persons and no adjustment for potential confounders
Thériault et al, 1990 (23)	Aluminum workers with >5–10 y exposure to tar volatiles who received a diagnosis of bladder cancer during the screening program (1980–1986) vs. before the screening program (1970–1979) in Quebec	Retrospective cohort study with historical control	Annual urine cytology	79 (30 screened and 49 not screened)	Screened patients vs. unscreened patients: Early-stage bladder cancer: 77% (23 of 30) vs. 67% (33 of 49); $P > 0.10$ Mortality (age-adjusted): RR, 0.54 (CI, 0.20–1.48)	Poor; historical cohort and no adjustment for potential confounders

OR = odds ratio; RR = relative risk.

patients and those who did not participate (1.3% vs. 1.2%), but clinical outcomes were not compared.

We identified 2 other studies that met inclusion criteria and were not included in the previous evidence review (**Table 1**). A cohort study found that in aluminum production workers exposed to volatile benzene-soluble coal tar–pitch chemicals, there were nonstatistically significant trends toward a higher proportion of early-stage bladder cancer at diagnosis (77% vs. 67%) and increased 5-year survival (RR, 0.54 [CI, 0.20 to 1.48]) after annual urine cytology screening was instituted than before the screening program (23). This study was rated poor-quality because it evaluated a historical control group and did not attempt to adjust or control for confounders. A case–control study found that persons who died of bladder cancer had lower odds of having received screening urinalysis in the previous 5 years, after adjustment for smoking status and occupational bladder cancer exposure (odds ratio [OR], 0.60 [CI, 0.41 to 0.87]) (21). This study was rated poor-quality because it could not accurately ascertain the reason that urinalyses were obtained.

Other prospective studies on bladder cancer screening did not meet inclusion criteria because they were uncontrolled but may provide some information about the yield of screening in different populations. Two European studies of older (age >60 years), average-risk men screened

with urine dipstick for hematuria found bladder cancer in 0.5% of persons (5 of 1096) (24) and 0.7% of persons (17 of 2356) (25). A study of higher-risk men and women with a smoking history of 40 pack-years or more found that 3.3% (6 of 183) had bladder cancer identified after 1-time screening with a battery of tests (urine dipstick, nuclear matrix protein-22 [NMP22], and cytology) (26). A study of higher-risk men and women with a history of smoking exceeding 10 years or a history of having a high-risk occupation for longer than 15 years found that 0.2% (3 of 1502) had bladder cancer after 1-time screening with a test for NMP22 (27). A study that periodically screened workers with occupational exposures to β-naphthylamine or benzidine with urinalysis, cytology, and urine biomarkers identified bladder cancer in 1.0% of persons (3 of 304) (28).

What Are the Accuracy and Reliability of Urinalysis for Hematuria, Urinary Cytology, and Other Urinary Biomarkers for Identification of Bladder Cancer? (Key Question 2)

No study evaluated the sensitivity and specificity of screening tests for bladder cancer in asymptomatic persons (**Table 2**). All studies, including those that did not focus on patients with previously diagnosed bladder cancer (29–31), enrolled patients with gross hematuria; urinary symptoms, such as dysuria; or both, typically in referral settings. Only 1 study provided data to calculate the diagnostic accuracy of the NMP22 compared with cystoscopy in a subgroup of patients without gross hematuria (with or without dysuria) (32). The study found a sensitivity of 0.45 (17 of 38 [CI, 0.29 to 0.62]) and specificity of 0.86 (889 of 1028 [CI, 0.84 to 0.88]), for a positive likelihood ratio of 3.3 (CI, 2.2 to 4.9) and negative likelihood ratio of 0.64 (CI, 0.48 to 0.85). The positive predictive value was 0.11 (17 of 156 [CI, 0.07 to 0.17]), with a bladder cancer prevalence of 4% (38 of 1066 [CI, 3% to 5%]). By comparison, the positive predictive value in patients with gross hematuria (bladder cancer prevalence of 18%) was 0.43 (26 of 61).

Six studies reported positive predictive values in screened asymptomatic patients but did not meet inclusion criteria because patients with negative screening tests did not undergo cystoscopy, and thus other markers of diagnostic accuracy could not be calculated (20, 24, 26–28, 33). The positive predictive value of screening (1-time testing for hematuria or NMP22) ranged from 3% to 5% in 3 studies (24, 27, 33) in which bladder cancer prevalence was less than 1%, including 1 study that enrolled higher-risk patients on the basis of smoking and occupational history (27). The positive predictive value was 8% in 3 studies in

Table 2. **Summary of Evidence**

Studies	Limitations	Consistency	Primary Care Applicability	Overall Quality
Is there direct evidence that screening for bladder cancer reduces morbidity or mortality? (KQ 1)				
3 poor-quality observational studies	No inception cohort of similar unscreened persons, historical control, or inaccurate ascertainment of exposures and symptoms	No important inconsistency	Low to moderate	Poor
Findings: No RCTs of screening for bladder cancer were identified. Three observational studies found that screening for bladder cancer was associated with decreased risk for bladder cancer mortality or lower stage at diagnosis (or trends toward decreased risks) but were difficult to interpret because of important methodological shortcomings.				
What are the accuracy and reliability of urinalysis for hematuria, urine cytology, and urine biomarkers for identification of bladder cancer? (KQ 2)				
0 studies	All studies enrolled patients with previous bladder cancer or signs and symptoms of bladder cancer	–	–	–
Findings: No studies evaluated the sensitivity or specificity of diagnostic tests for bladder cancer in patients without previous bladder cancer or signs and symptoms associated with bladder cancer. Six studies found a positive predictive value <10% for screening in asymptomatic persons, including high-risk populations.*				
Does treatment of screen-detected bladder cancer reduce morbidity and mortality from this disease? (KQ 3)				
0 studies	No studies met inclusion criteria	–	–	–
Findings: No evidence. No RCTs or controlled observational studies were identified.				
What are the harms of screening for bladder cancer or treatment of screen-detected bladder cancer? (KQ 4)				
0 studies	No studies met inclusion criteria	–	–	–
Findings: No RCTs or controlled observational studies were identified. Harms of screening are likely to be related to the false-positive rate (see KQ 2). One large, uncontrolled observational study of transurethral resection of bladder tumor reported bleeding events in 2.8% and perforation in 1.3%, with no associated mortality.				

KQ = key question; RCT = randomized, controlled trial.
* These studies did not meet formal inclusion criteria because they provided incomplete diagnostic information.

which the prevalence of bladder cancer ranged from 1% to 3%, on the basis of screening with repeated urinalysis or 1-time screening with several tests (urinalysis, cytology, and urine biomarkers) (20, 26, 28); one of these studies included persons with high-risk occupational exposure (28).

Does Treatment of Screen-Detected Bladder Cancer Reduce Morbidity and Mortality From This Disease? (Key Question 3)

We identified no randomized trials or controlled observational studies of treatment of screen-detected or superficial bladder cancer compared with no treatment (**Table 2**).

What Are the Harms of Screening for Bladder Cancer or Treatment of Screen-Detected Bladder Cancer? (Key Question 4)

Potential harms of screening for bladder cancer can occur in the evaluation of positive tests or with subsequent treatments. Follow-up of positive screening results typically includes cystoscopy and may include imaging studies. Potential harms include anxiety, labeling, discomfort or pain related to cystoscopy, and complications related to cystoscopy and biopsy (such as perforation, bleeding, or infection) and imaging (such as effects related to use of intravenous contrast) (34–37). Screening could also increase the overall exposure to additional procedures and treatments due to earlier initiation of routine surveillance and frequent tumor recurrence.

We identified no controlled studies that directly measured harms associated with screening for bladder cancer (**Table 2**). In lower-prevalence populations, more patients would be exposed to unnecessary potential for harm due to higher false-positive rates of screening compared with higher-prevalence populations. However, we found no studies estimating the magnitude of harms associated with unnecessary procedures.

We also identified no controlled studies comparing harms of treatment of screen-detected bladder cancer versus no treatment. Although 1 large (2821 participants), uncontrolled observational study reported rates of bleeding (2.8%) and perforation (1.3%) with transurethral resection of bladder tumor, it is not possible to estimate the incremental harms that may have occurred owing to screening from these data (38).

Discussion

Table 2 summarizes the results of this evidence synthesis, by key question. Bladder cancer is 1 of the 10 most frequently diagnosed types of cancer in the United States. Circumstances that favor screening include the presence of a prolonged asymptomatic phase in which superficial types of bladder cancer at high risk for progression can be detected, availability of accurate screening tests, and availability of effective and safe treatments. Evidence on the natural history of asymptomatic bladder cancer is lacking because tumors are typically treated after diagnosis (14). In addition, variability in the natural history of bladder cancer, with respect to risk for tumor progression from superficial to muscle-invasive or metastatic bladder cancer and the relatively low incidence of bladder cancer mortality relative to the incidence of new cases, present challenges in evaluating potential benefits and harms of screening (7, 14). Major gaps in the evidence make it impossible to reach any reliable conclusions about screening. We identified no high-quality RCTs or controlled observational studies showing that bladder cancer screening is associated with improved clinical outcomes compared with no screening. The only controlled cohort studies on screening suggest that screening might result in a shift to earlier stage bladder cancer diagnoses or reduce the long-term risk for bladder-cancer–related death, but the studies had serious methodological shortcomings, including selection of noncomparable control groups and failure to adjust for potential confounders (20, 23).

In terms of indirect evidence, we could not estimate the effectiveness of treatments for screen-detected bladder cancer because no studies compared clinical outcomes associated with treatment versus no treatment. Evidence on the diagnostic accuracy of screening tests in asymptomatic patients without a history of bladder cancer is limited to studies reporting positive predictive values without data on sensitivity or specificity. Many recent studies have evaluated urinary biomarkers, but their main focus has been on diagnostic accuracy for recurrent bladder cancer or in patients with gross hematuria or lower urinary tract symptoms, rather than in asymptomatic persons relevant for screening. In screening studies, the positive predictive value of various tests is less than 10%, even in higher-risk populations, which could result in unnecessary procedures and associated harms (24, 26–28, 33). However, there are no reliable data to estimate the incremental harms associated with screening for bladder cancer compared with no screening, or the harms associated with treatment of screen-detected bladder cancer versus no treatment.

Randomized trials or appropriately designed cohort studies are needed to understand the effects of screening compared with no screening on clinical outcomes. It would be appropriate to focus initial randomized trials on higher-risk groups based on smoking status, demographic characteristics, workplace exposures, or other factors because the greater prevalence of bladder cancer could result in a higher yield from screening and allow researchers to enroll smaller sample sizes. If randomized trials show benefit in high-risk groups, future trials could evaluate testing of all asymptomatic persons. In lieu of randomized trials, cohort studies could be helpful for understanding risks and benefits of screening, but they should be designed with appropriate attention to potential confounding and selection of appropriate control groups to be more informative than current studies. If screening is shown to be effective, studies should evaluate the comparative diagnostic accuracy of urine tests for hematuria, urinary cytology, and urinary biomarkers in

asymptomatic patients in order to better inform the selection of screening tests.

From Oregon Health & Science University, Portland, Oregon.

Acknowledgment: The authors thank Agency for Healthcare Research and Quality Medical Officer Iris Mabry-Hernandez, MD, MPH, for commenting on draft versions of this manuscript and Thomas G. DeWitt, MD; Diana B. Petitti, MD, MPH; and Timothy J. Wilt, MD, MPH, who served as the USPSTF leads for this project. The authors also thank Christina Bougatsos, BS, for assistance with the manuscript.

Grant Support: By the Agency for Healthcare Research and Quality (contract no. HHSA-290-2007-10057-I-EPC3, Task Order Number 3).

Potential Conflicts of Interest: Dr. Chou has disclosed the following: *Grants received/pending:* Agency for Healthcare Research and Quality; *Support for travel to meetings for the study or other purposes:* Agency for Healthcare Research and Quality. Ms. Dana has disclosed the following: *Grants received/pending:* Agency for Healthcare Research and Quality. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M10-1071.

Requests for Single Reprints: Roger Chou, MD, Oregon Health & Science University, Mailcode BICC, 3181 Southwest Sam Jackson Park Road, Mailcode BICC, Portland, OR 97239; e-mail, chour@ohsu.edu.

Current author addresses and author contributions are available at www.annals.org.

References

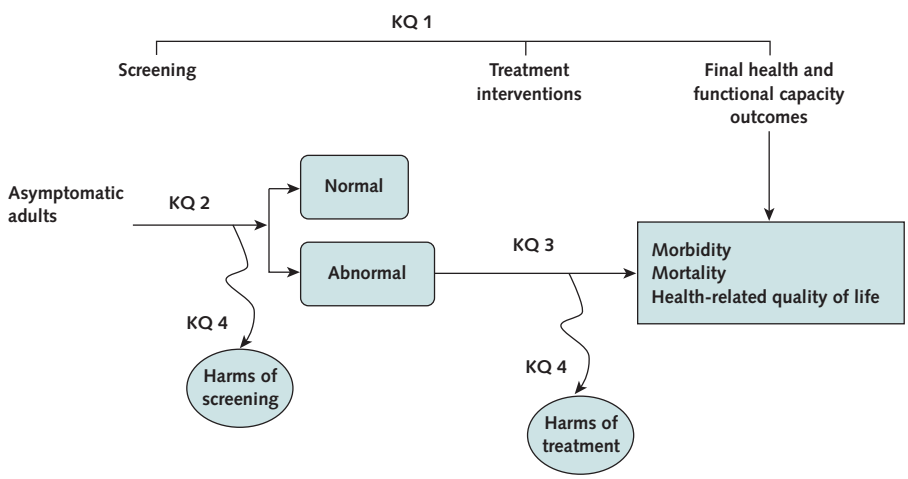
1. **U.S. Cancer Statistics Working Group.** U.S. Cancer Statistics: 1999–2005. Incidence and Mortality Web-based Report. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2009. Accessed at www.cdc.gov/uscs on 14 December 2009.
2. **Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ.** Cancer statistics, 2009. CA Cancer J Clin. 2009;59:225-49. [PMID: 19474385]
3. **Kiemeney LA.** Hereditary bladder cancer. Scand J Urol Nephrol Suppl. 2008: 110-5. [PMID: 18815925]
4. **Kirkali Z, Chan T, Manoharan M, Algaba F, Busch C, Cheng L, et al.** Bladder cancer: epidemiology, staging and grading, and diagnosis. Urology. 2005; 66:4-34. [PMID: 16399414]
5. **Olfert SM, Felknor SA, Delclos GL.** An updated review of the literature: risk factors for bladder cancer with focus on occupational exposures. South Med J. 2006;99:1256-63. [PMID: 17195421]
6. **Wu X, Ros MM, Gu J, Kiemeney L.** Epidemiology and genetic susceptibility to bladder cancer. BJU Int. 2008;102:1207-15. [PMID: 19035883]
7. **Kaufman DS, Shipley WU, Feldman AS.** Bladder cancer. Lancet. 2009;374: 239-49. [PMID: 19520422]
8. **National Cancer Institute; U.S. National Institutes of Health.** Bladder cancer treatment. General information about bladder cancer. Accessed at www.cancer.gov/cancertopics/pdq/treatment/bladder on 14 December 2009.
9. **Pashos CL, Botteman MF, Laskin BL, Redaelli A.** Bladder cancer: epidemiology, diagnosis, and management. Cancer Pract. 2002;10:311-22. [PMID: 12406054]
10. **American Cancer Society.** Bladder cancer detailed guide. Accessed at www.cancer.org/docroot/CRI/CRI_2_3x.asp?dt=44 on 14 December 2009.
11. **American Joint Committee on Cancer.** What is cancer staging? 2009. Accessed at www.cancerstaging.org/mission/whatis.html on 14 December 2009.
12. **Konety BR, Joyce GF, Wise F.** Bladder and upper tract urothelial cancer. In: Litwin MS, Saigal. CS, eds. Urologic Diseases in America. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Washington, DC: U.S. Government Printing Office; 2007. NIH publication no. 07-5512.
13. **Hall MC, Chang SS, Dalbagni G, Pruthi RS, Seigne JD, Skinner EC, et al.** Guideline for the management of nonmuscle invasive bladder cancer (stages Ta, T1, and Tis): 2007 update. J Urol. 2007;178:2314-30. [PMID: 17993339]
14. **Epstein JI, Amin MB, Reuter VR, Mostofi FK.** The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Bladder Consensus Conference Committee. Am J Surg Pathol. 1998;22:1435-48. [PMID: 9850170]
15. **Madeb R, Golijanin D, Knopf J, Messing EM.** Current state of screening for bladder cancer. Expert Rev Anticancer Ther. 2007;7:981-7. [PMID: 17627458]
16. **RTI International-University of North Carolina Evidence-based Practice Center.** Screening for Bladder Cancer. Brief Evidence Update (Prepared by RTI International-University of North Carolina Evidence-based Practice Center for the U.S. Preventive Services Task Force. Agency for Healthcare Research and Quality.) Rockville, MD: Agency for Healthcare Research and Quality; 2004. Accessed at www.uspreventiveservicestaskforce.org/3rduspstf/bladder/blacanup.htm on 18 August 2010.
17. **National Cancer Institute.** SEER Cancer Statistics Review 1975-2007. Accessed at http://seer.cancer.gov/csr/1975_2007/results_merged/sect_27_urinary_bladder.pdf on 30 April 2010.
18. **Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al; Methods Work Group, Third US Preventive Services Task Force.** Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20:21-35. [PMID: 11306229]
19. **Leeflang MM, Deeks JJ, Gatsonis C, Bossuyt PM; Cochrane Diagnostic Test Accuracy Working Group.** Systematic reviews of diagnostic test accuracy. Ann Intern Med. 2008;149:889-97. [PMID: 19075208]
20. **Messing EM, Young TB, Hunt VB, Gilchrist KW, Newton MA, Bram LL, et al.** Comparison of bladder cancer outcome in men undergoing hematuria home screening versus those with standard clinical presentations. Urology. 1995; 45:387-96. [PMID: 7879333]
21. **Friedman GD, Hiatt RA, Quesenberry CP Jr, Selby JV, Weiss NS.** Problems in assessing screening experience in observational studies of screening efficacy: example of urinalysis screening for bladder cancer. J Med Screen. 1995;2: 219-23. [PMID: 8719152]
22. **Messing EM, Madeb R, Young T, Gilchrist KW, Bram L, Greenberg EB, et al.** Long-term outcome of hematuria home screening for bladder cancer in men. Cancer. 2006;107:2173-9. [PMID: 17029275]
23. **Thériault GP, Tremblay CG, Armstrong BG.** Bladder cancer screening among primary aluminum production workers in Quebec. J Occup Med. 1990; 32:869-72. [PMID: 2074510]
24. **Hedelin H, Jonsson K, Salomonsson K, Boman H.** Screening for bladder tumours in men aged 60-70 years with a bladder tumour marker (UBC) and dipstick-detected haematuria using both white-light and fluorescence cystoscopy. Scand J Urol Nephrol. 2006;40:26-30. [PMID: 16452052]
25. **Whelan P, Britton JP, Dowell AC.** Three-year follow-up of bladder tumours found on screening. Br J Urol. 1993;72:893-6. [PMID: 8306152]
26. **Steiner H, Bergmeister M, Verdorfer I, Granig T, Mikuz G, Bartsch G, et al.** Early results of bladder-cancer screening in a high-risk population of heavy smokers. BJU Int. 2008;102:291-6. [PMID: 18336612]
27. **Lotan Y, Elias K, Svatek RS, Bagrodia A, Nuss G, Moran B, et al.** Bladder cancer screening in a high risk asymptomatic population using a point of care urine based protein tumor marker. J Urol. 2009;182:52-7. [PMID: 19450825]
28. **Marsh GM, Cassidy LD.** The Drake Health Registry Study: findings from fifteen years of continuous bladder cancer screening. Am J Ind Med. 2003;43: 142-8. [PMID: 12541268]
29. **Grossman HB, Messing E, Soloway M, Tomera K, Katz G, Berger Y, et al.** Detection of bladder cancer using a point-of-care proteomic assay. JAMA. 2005; 293:810-6. [PMID: 15713770]
30. **Ponsky LE, Sharma S, Pandrangi L, Kedia S, Nelson D, Agarwal A, et al.** Screening and monitoring for bladder cancer: refining the use of NMP22. J Urol. 2001;166:75-8. [PMID: 11435827]
31. **Zippe C, Pandrangi L, Agarwal A.** NMP22 is a sensitive, cost-effective test in patients at risk for bladder cancer. J Urol. 1999;161:62-5. [PMID: 10037369]
32. **Lotan Y, Capitanio U, Shariat SF, Hutterer GC, Karakiewicz PI.** Impact of clinical factors, including a point-of-care nuclear matrix protein-22 assay and cytology, on bladder cancer detection. BJU Int. 2009;103:1368-74. [PMID: 19338566]
33. **Britton JP, Dowell AC, Whelan P.** Dipstick haematuria and bladder cancer

in men over 60: results of a community study. BMJ. 1989;299:1010-2. [PMID: 2511941]
34. **Aaronson DS, Walsh TJ, Smith JF, Davies BJ, Hsieh MH, Konety BR.** Meta-analysis: does lidocaine gel before flexible cystoscopy provide pain relief? BJU Int. 2009;104:506-9. [PMID: 19239453]
35. **Burke DM, Shackley DC, O'Reilly PH.** The community-based morbidity of flexible cystoscopy. BJU Int. 2002;89:347-9. [PMID: 11872022]
36. **Stav K, Leibovici D, Goren E, Livshitz A, Siegel YI, Lindner A, et al.** Adverse effects of cystoscopy and its impact on patients' quality of life and sexual performance. Isr Med Assoc J. 2004;6:474-8. [PMID: 15326827]
37. **Turan H, Balci U, Erdinc FS, Tulek N, Germiyanoglu C.** Bacteriuria, pyuria and bacteremia frequency following outpatient cystoscopy. Int J Urol. 2006;13:25-8. [PMID: 16448428]
38. **Collado A, Chéchile GE, Salvador J, Vicente J.** Early complications of endoscopic treatment for superficial bladder tumors. J Urol. 2000;164:1529-32. [PMID: 11025697]

Current Author Addresses: Dr. Chou and Ms. Dana: 3181 Southwest Sam Jackson Park Road, Mailcode BICC, Portland, OR 97239.

Author Contributions: Conception and design: R. Chou, T. Dana.
Analysis and interpretation of the data: R. Chou, T. Dana.
Drafting of the article: R. Chou.
Critical revision of the article for important intellectual content: R. Chou, T. Dana.
Final approval of the article: R. Chou.
Statistical expertise: R. Chou.
Obtaining of funding: R. Chou.
Administrative, technical, or logistic support: R. Chou, T. Dana.
Collection and assembly of data: R. Chou, T. Dana.

Appendix Figure. **Analytic framework.**



Key Questions
1. Is there direct evidence that screening for bladder cancer reduces morbidity or mortality?
2. What are the accuracy and reliability of urinalysis, urinary cytology, and other urinary biomarkers for identification of bladder cancer?
3. Does treatment of screen-detected bladder cancer reduce morbidity and mortality from this disease?
4. What are the harms of screening for bladder cancer and treatment of screen-detected bladder cancer?

KQ = key question.

Appendix Table 1. Search Strategies

Overall

Database: CancerLit subsection of PubMed
Search strategy:
1. bladder cancer.mp. or Urinary Bladder Neoplasms/
2. mass screening.mp. or Mass Screening/
3. 1 and 2
4. limit 3 to cancer
5. from 4 keep 1-182

EBM Reviews: Cochrane Central Register of Controlled Trials
Search strategy:
1. (bladder adj2 (cancer$ or malign$ or tumor$ or neoplas$ or carcino$ or adenocarcino$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
2. screen$.mp.
3. (routine$ adj3 (test$ or detect$ or find$ or diagno$)).mp.
4. 2 or 3
5. 1 and 4
6. (mortal$ or death$ or fatal$ or dead).mp.
7. morbid$.mp.
8. 6 or 7
9. 8 and 1
10. (accura$ or inaccura$ or reliab$ or unreliab$ or incorrect$ or (false$ adj3 (positiv$ or negativ$))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
11. (diagnos$ adj3 (mistak$ or error$ or erroneous$ or wrong$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
12. (differential$ adj2 diagnos$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
13. 10 or 11 or 12
14. 1 and 13
15. ((gene or genet$ or DNA) adj2 (test or tests or testing or tested)).mp.
16. biomarker$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
17. 15 or 16
18. 17 and 1
19. ((early or earli$ or time$) adj5 (detect$ or diagnos$ or discover$)).mp.
20. 1 and 19
21. 14 or 18 or 9 or 20 or 5
22. from 21 keep 1-143

EBM Reviews: Cochrane Database of Systematic Reviews
Search strategy:
1. (bladder adj2 (cancer$ or malign$ or tumor$ or neoplas$ or carcino$ or adenocarcino$)).mp. [mp=title, abstract, full text, keywords, caption text]
2. screen$.mp.
3. (routine$ adj3 (test$ or detect$ or find$ or diagno$)).mp.
4. 2 or 3
5. 1 and 4
6. (mortal$ or death$ or fatal$ or dead).mp.
7. morbid$.mp.
8. 6 or 7
9. 8 and 1
10. (accura$ or inaccura$ or reliab$ or unreliab$ or incorrect$ or (false$ adj3 (positiv$ or negativ$))).mp. [mp=title, abstract, full text, keywords, caption text]
11. (diagnos$ adj3 (mistak$ or error$ or erroneous$ or wrong$)).mp. [mp=title, abstract, full text, keywords, caption text]
12. (differential$ adj2 diagnos$).mp. [mp=title, abstract, full text, keywords, caption text]
13. 10 or 11 or 12
14. 1 and 13
15. ((gene or genet$ or DNA) adj2 (test or tests or testing or tested)).mp.
16. biomarker$.mp. [mp=title, abstract, full text, keywords, caption text]
17. 15 or 16
18. 17 and 1
19. ((early or earli$ or time$) adj5 (detect$ or diagnos$ or discover$)).mp.
20. 1 and 19
21. 14 or 18 or 9 or 20 or 5
22. from 21 keep 1-39

Screening

Database: Ovid MEDLINE
Search strategy:
1. exp Urinary Bladder Neoplasms/
2. exp Mass Screening/
3. 1 and 2
4. exp Urinary Bladder Neoplasms/pa, ri, us, di, ra, pc
5. screen$.mp.
6. 4 and 5
7. 6 or 3
8. exp Vital Statistics/
9. 8 and 7
10. morbid$.mp.
11. (mortal$ or death$ or fatal$ or dead).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
12. mo.fs.
13. 11 or 10 or 12
14. 7 and 13
15. 9 or 14
16. (200$ not (2000$ or 2001$)).ed.
17. 16 and 15
18. from 17 keep 1-48

Diagnostic accuracy

Database: Ovid MEDLINE
Search strategy:
1. exp Urinary Bladder Neoplasms/
2. exp Urinary Bladder Neoplasms/di
3. exp Urinary Bladder Neoplasms/ge
4. exp "Sensitivity and Specificity"/
5. 3 or 2
6. 4 and 5
7. (accura$ or inaccura$ or reliab$ or unreliab$ or incorrect$ or (false$ adj3 (positiv$ or negativ$))).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
8. 5 and 7
9. exp Diagnostic Errors/
10. 9 and 5
11. exp Diagnosis, Differential/
12. 11 and 5
13. exp biomarkers/
14. 5 and 13
15. exp mass screening/or screen$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
16. (routine$ adj3 (test$ or detect$ or find$ or diagno$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
17. 15 or 16
18. 6 or 8 or 10 or 12 or 14
19. 17 and 18
20. (200$ not (2000$ or 2001$)).ed.
21. 19 and 20
22. from 21 keep 1-115

Treatment

Database: Ovid MEDLINE
Search strategy:
1. exp Urinary Bladder Neoplasms/th, rt, dh, su, dt [Therapy, Radiotherapy, Diet Therapy, Surgery, Drug Therapy]
2. ((early or earli$) adj5 (detect$ or diagnos$ or discover$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

Continued on following page

Appendix Table 1—Continued

3. 1 and 2
4. exp Time/
5. 4 and 1
6. exp Prognosis/
7. exp "Outcome Assessment (Health Care)"/
8. 6 or 7
9. 8 and 5
10. exp neoplasm staging/
11. 1 and 4 and 10
12. exp Vital Statistics/
13. morbid$.mp.
14. (mortal$ or death$ or fatal$ or dead).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
15. mo.fs.
16. 13 or 15 or 12 or 14
17. 16 and 5
18. 9 or 11 or 17
19. 3 or 18
20. from 19 keep 1-421

Appendix Table 2. Inclusion and Exclusion Criteria

Settings

Includes studies of screening done in settings generalizable to primary care and studies of diagnostic accuracy done in specialty settings if the screening test is generalizable to primary care

Excludes specialty settings and countries with populations not similar to the United States

Populations

Includes adults ≥50 y

Excludes previous bladder cancer, gross hematuria, and urinary symptoms

Screening tests

Includes screening tests used or available in primary care settings (urine dipstick or urinalysis for microscopic hematuria, urine cytology, and urine biomarkers for bladder cancer)

Excludes cystoscopy (except as gold standard examination)

Interventions

Includes surgery, radiation therapy, chemotherapy, biologic therapy (biotherapy, immunotherapy), and photodynamic therapy

Outcomes

Includes morbidity, mortality, and health-related quality of life

Study types

Includes randomized, controlled trials of screening vs. no screening or treatment vs. no treatment; cohort and case–control studies of screening vs. no screening or treatment vs. no treatment; high-quality systematic reviews; and studies of diagnostic accuracy in which the screening test is compared with a reference standard (cystoscopy)

Excludes case series and nonsystematic reviews

Appendix Table 3. U.S. Preventive Services Task Force Quality Rating Criteria for RCTs and Observational Studies

Diagnostic accuracy studies

- Criteria
  - Screening test is relevant, available for primary care, and adequately described
  - Study uses a credible reference standard and is done regardless of test results
  - Reference standard is interpreted independently of the screening test
  - Handles indeterminate results in a reasonable manner
  - Spectrum of patients included in study
  - Sample size
  - Administration of reliable screening test
  - Random or consecutive selection of patients (19)
  - Screening cutoff is predetermined (19)
  - All patients undergo the reference standard (19)
- Definition of ratings (based on criteria)
  - Good: Evaluates a relevant available screening test; uses a credible reference standard; interprets a reference standard independently of the screening test; reliability of the test is assessed; has few or handles indeterminate results in a reasonable manner; includes a large number (>100) of broad-spectrum patients with and without disease; attempts to enroll a random or consecutive sample of patients who meet inclusion criteria (19); and screening cutoffs are prestated (19)
  - Fair: Evaluates a relevant available screening test; uses a reasonable although not the best standard; interprets a reference standard independent of the screening test; includes a moderate sample size (50–100 persons) and a medium spectrum of patients (i.e., applicable to most screening settings)
  - Poor: Has an important limitation, such as use of an inappropriate reference standard; the screening test is improperly administered; has a biased ascertainment of the reference standard; and includes a very small sample size or very narrow selected spectrum of patients

RCTs and cohort studies

- Criteria
  - Initial assembly of similar groups
    - RCTs: Adequate randomization, including concealment and whether potential confounders were distributed equally among groups
    - Cohort studies: Consideration of potential confounders with either restriction or measurement for adjustment in the analysis and consideration of inception cohorts
  - Maintenance of similar groups (includes attrition, crossovers, adherence, and contamination)
  - Important differential loss to follow-up or overall high loss to follow-up
  - Measurements: equal, reliable, and valid (includes masking of outcome assessment)
  - Clear definition of interventions
  - Important outcomes considered
  - Analysis: adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs; for cluster RCTs, correction for correlation coefficient
- Definition of ratings (based on criteria)
  - Good: Meets all criteria: Similar groups are assembled initially and maintained throughout the study (follow-up ≤80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention is given to confounders in analysis
  - Fair: Any or all of the following problems occur without the important limitations noted in the poor category: Generally similar groups are assembled initially, but some question remains about whether some (although not major) differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for
  - Poor: Any of the following major limitations exists: Groups assembled initially are not close to being similar or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention

Case–control studies

- Criteria
  - Accurate ascertainment of cases
  - Nonbiased selection of case patients and control participants, with exclusion criteria applied equally to both
  - Response rate
  - Diagnostic testing procedures applied equally to each group
  - Measurement of exposure accurate and applied equally to each group
  - Appropriate attention to potential confounding variables
- Definition of ratings (based on criteria)
  - Good: Appropriate ascertainment of cases and nonbiased selection of case patients and control participants; exclusion criteria applied equally to case patients and control participants; response rate ≥80%; diagnostic procedures and measurements accurate and applied equally to case patients and control participants; and appropriate attention given to confounding variables
  - Fair: Recent, relevant, without major apparent selection or diagnostic work-up bias but with response rate <80% or attention to some but not all important confounding variables
  - Poor: Major selection or diagnostic work-up biases, response rate <50%, or inattention to confounding variables

RCT = randomized, controlled trial.