Should We Screen for Bladder Cancer in a High-Risk Population?

A Cost Per Life-Year Saved Analysis

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BACKGROUND. The U.S. Food and Drug Administration recently approved screening high-risk patients for bladder cancer using urine-based markers. The cost and life-years saved associated with bladder cancer screening were evaluated.

METHODS. A Markov model was created to estimate cumulative cancer-related costs and efficacy of screening (vs. no screening) of a high-risk population for bladder cancer using a urine-based tumor marker over a 5-year period. Assumptions were based on literature review of survival and progression rates for patients with bladder cancer and costs associated with different bladder cancer disease states.

RESULTS. Screening for bladder cancer in a population with a 4% incidence of bladder cancer resulted in a gain of 3.0 life years per 1000 subjects at a cost savings of $101,000 for the population, assuming a 50% downstaging in the screened population from muscle-invasive to nonmuscle-invasive disease. One-way sensitivity analyses found that screening is the most cost-effective strategy if cancer incidence is >1.6%, tumor marker costs <$126, marker sensitivity is >26%, marker specificity is >54%, downstaging with screening is >20%, and office cystoscopy costs <$694. Varying costs of cystectomy, transurethral resection of bladder tumor (TURBT), chemotherapy, end-of-life care, costs of metastatic disease, and a computed tomography scan over a wide range did not affect the superiority of screening.

CONCLUSIONS. The model found that urine-based markers are cost-effective in a high-risk population. Prospective randomized trials in a completely asymptomatic high-risk cohort are indicated before bladder cancer screening can be recommended. *Cancer* 2006;107:982–90. © *2006 American Cancer Society.*

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Cancer screening is generally considered a valuable tool to save lives but at this time it is limited to prostate, breast, colon, and cervical cancer. There are several factors that limit the effectiveness of cancer screening, including questions regarding survival benefit, disease prevalence, screening efficacy, and cost. One must ask why we do not screen for bladder cancer in high-risk persons such as heavy cigarette smokers or patients exposed to industrial chemicals. Smoking accounts for approximately half of bladder cancers diagnosed among men and approximately one-third of women.[1] Moreover, bladder cancer is the fourth most prevalent cancer in males and the ninth most prevalent cancer in females and is the most costly cancer from diagnosis to death.[2,3] When one compares disease prevalence and death rates, bladder cancer is significantly more common and has a higher mortality than cervical cancer (with 63,210 cases

and 13,180 deaths versus 10,370 cases and 3710 deaths estimated for 2005, respectively).[2] The best possibility for reducing bladder cancer mortality is early detection. Survival rates for bladder cancers are stage-dependent and 5-year survival for tumors confined to the mucosa are significantly higher than for cancers that are muscle-invasive or metastatic.[4] Because 25% of bladder tumors are diagnosed beyond the superficial cancer stage, a screening program that leads to earlier detection can decrease mortality.[5] Downstaging of bladder cancer with screening has been demonstrated using hematuria screening by Messing et al.[6] Only 4.8% of tumors in an asymptomatic screening group age >50 years were muscle-invasive compared with 23.9% in an unscreened population. Use of urine dipstick testing for hematuria is cheap and noninvasive but has a positive predictive value of only 5%, which limits its utility.[7,8] Other urine-based bladder markers such as NMP22 have been shown to have superior sensitivity and specificity as compared with hemoglobin dipstick.[9]

Recently, the Food and Drug Administration (FDA) approved the use of several urine-based tumor markers such as BladderChek (Matritech, Newton, MA) for diagnosis of bladder cancer in high-risk patients. BladderChek (NMP22) is a point-of-care test that provides immediate results and does not require a clinical laboratory for evaluation. A multiinstitutional study by Grossman et al.[10] utilized NMP22 to evaluate urine specimens from a large cohort of patients at elevated risk for bladder cancer due to factors such as age, history of smoking, or hematuria. They found cancer in 6% of their cohort and NMP22 rendered a sensitivity, specificity, and positive predictive value (PPV) of 55.7%, 85.7%, and 19.7%, respectively.

The purpose of this analysis was to assess the cost-effectiveness in terms of cost per life-years saved associated with implementing a screening program using bladder markers such as NMP22 in a high-risk population.

MATERIALS AND METHODS
Markov Decision Analysis
A Markov decision analysis model was created to estimate the cumulative cancer-related survival and costs for a population screened or not screened for bladder cancer with NMP22 (BladderChek) over a 5-year period. The Markov model was designed with TREEAGE PRO HEALTHCARE (Treeage Software, Williamstown, MA). The model assumes a subject to enter at age 50 years at high risk for bladder cancer due to heavy smoking or significant occupational exposure. The model allows varying the baseline age of screening by

modifying mortality due to other causes. Patients in the standard group will either have cancer or no cancer at a rate dependent on cancer incidence. Those subjects found to have bladder tumor(s) are treated with a transurethral resection and enter 1 of 4 bladder cancer disease states: 1) low-grade superficial (American Joint Committee on Cancer [AJCC] Stage T0, Tis, T1); 2) high-grade superficial (AJCC Stage T0, Tis, T1); 3) muscle invasive (AJCC Stage T2-T4); or 4) metastatic disease. We assumed a simple model of disease progression that occurs in a fixed sequence of health states. At the conclusion of each 12-month cycle, the patient could be considered disease-free and undergo routine surveillance, experience recurrence or progression of their disease, or die of unrelated causes. Patients with metastatic disease can die of their disease, die of other causes, or remain in the metastatic state. Patients with high-grade superficial disease received bacillus Calmette–Guerin (BCG) treatment. Patients diagnosed with muscle-invasive disease underwent immediate radical cystectomy with pelvic lymph node dissection. Twenty-five percent of patients with muscle-invasive disease have lymph node involvement and were assumed to undergo treatment with chemotherapy.[11,12] Patients diagnosed with metastatic disease received 4 cycles of chemotherapy (methotrexate, vinblastine, doxorubicin, and cisplatin [MVAC] or cisplatin/gemcitabine). In the screened population, the base case is screened 1 time at study entry; however, we also examined the model with annual and biannual screening. Subjects with a positive BladderChek test were evaluated with an office visit, cystoscopy, and urine cytology. Patients with a true-positive screen entered into 1 of the 4 cancer disease states as above but a proportion of the muscle-invasive cancers was downstaged to superficial disease. Those patients with a false-negative screen had cancer diagnosed in standard fashion and did not benefit from downstaging. Patients with a false-positive screen accrued the costs of screening but had the same survival as those with no cancer.

Assumptions
All model assumptions are displayed in Table 1. Bladder cancer incidence rates for a high-risk population were derived from a study by Grossman et al.[10] evaluating the utility of the BladderChek test among a large cohort of patients at elevated risk for bladder cancer due to factors such as age, history of smoking, or hematuria. They found cancer in 6% of their cohort over a 9-month period. We assumed an annual baseline cancer incidence of 4% in the model because a portion of the patients in the Grossman et al. study had hematuria and we are modeling a purely asymptomatic high-risk screening population. Sensitivity analyses were used to

TABLE 1
Model Assumptions

Variable	Base case	Range	One-way sensitivity cost-effectiveness threshold
Cancer incidence[10]	4%	0.1–8%	1.6%
Cost parameters			
NMP22 test[10]	$24	$1–1000	$126
Office cystoscopy*	$206	0–$1000	$694
Cytology*	$56	$50–750	†
Intravenous pyelogram‡	$126	0–$1000	†
CT scan abdomen/pelvis‡	$337	$100–3000	†
Office visit level 3 (established)*	$55	0–$500	†
TURBT‡	$3,812	$1000–$10,000	†
BCG	$1,620	$100–5000	†
Cystectomy‡	$22,292	$10,000–$50,000	†
Chemotherapy‡	$43,000	$10,000–100,000	†
Yearly cost of metastatic disease	$500	0–$3000	†
Last 6 mos of life	$50,000	$10,000–500,000	†
Discount rate[21]	3%	0–10%	†
Marker accuracy			
Sensitivity			
Low grade[9]	.61(.35–.81)	.5–1	†
High grade[9]	.79 (.63–.89)	.5–1	26%
Specificity[10]	.86 (.84–.88)	.1–1	54%
Downstaging with screening[6]	50%	10–100%	20%
Yearly rate of death from other causes[20]	0.65%	0–20%	†

CT indicates computed tomography; TURBT, transurethral resection of bladder tumor; BCG, bacillus Calmette–Guerin.

* Medicare reimbursement 2005.

† Screening was more cost-effective over entire variable range.

‡ Local hospital cost.

TABLE 2
Recurrence, Progression, and Death Rates for Different Stages of Bladder Cancer

	Yearly %				
	1	2	3	4	5
Recurrence, superficial stage[13,14]					
Low-grade	30	10	5	5	5
High-grade	35	15	5	3	3
Progression, superficial stage[13,14,18,23]					
Low-grade	4	2	2	1	1
High-grade	10	10	5	3	2
Progression to metastases after cystectomy[11,12]	25	13	8	4	4
Death from bladder cancer in patients with metastatic disease after chemotherapy[19]	42	80	50		

model various cancer incidence rates. The model assumes that all cancers will become symptomatic and be diagnosed based on the fact that bladder cancer is rarely first discovered at the time of autopsy. The bladder cancer AJCC stage distribution was based on the National Cancer Database including over 70,000 patients: Stage 0 (44.3%), Stage I (28.9%), Stage II (12.9%), Stage III (7%), and Stage IV (6.9%).[4] The grade distribution for patients with T0 and T1 disease was 29%, 52.6%, and 18.4% for WHO Grades 1, 2, and 3, respectively, based on weighted means derived from 6 articles involving 4514 patients.[13–18] In patients with T2 disease and higher, 90% of patients had high-grade disease.[11] Cancer recurrence and progression rates depend heavily on the stage of disease. A literature review was performed to determine risks of recurrence and progression for patients with superficial disease, risk of

progression in patients after cystectomy, and risk of death for patients with metastases after chemotherapy (Table 2). Weighted means were utilized to determine recurrence and progression rates when more than 1 study was utilized. Cancer-specific death rates in patients with metastatic disease who received chemotherapy were obtained from a large multicenter Phase III study.[19] The yearly risk of dying from other causes was based on life-tables from the National Center for Health Statistics.[20]

The model assumed a baseline rate of downstaging of 50%. This is a conservative estimate of risk reduction based on published data regarding hematuria screening for bladder cancer by Messing et al.[6] In that analysis, only 4.8% of patients identified during screening had muscle-invasive disease compared with 23.9% in an unscreened population, an 80% risk reduction. Screening was assumed to lead to a downstaging but not downgrading, so muscle-invasive cancers that were high grade were assumed to be downstaged to superficial high-grade cancers.[6] Those tumors that are downstaged will still recur and progress in the Markov model at a rate dependent on their stage and grade. Marker sensitivity for different grade and stage disease was obtained from metaanalysis of the literature including 15 studies for NMP22.[9] Specificity was obtained from an evaluation of 1331 patients at elevated risk for bladder cancer due to factors such as age, history of smoking, or hematuria.[10]

Costs

Cost data are shown in Table 1. All data were collected from cost, not charge, data. All costs were updated to 2005 U.S. dollars with the Gross Domestic Product Deflator Inflation Calculator (available at URL: http://

www1.jsc.nasa.gov/bu2/inflateGDP.html). A 3% annual discount rate was applied to all future costs and benefits.[21] Discounting is necessary when the experience of the patient in the near term is valued more than future costs and health outcomes. The transurethral resection of bladder tumor (TURBT) and cystectomy costs were based on the mean total costs for 60 and 37 consecutive patients in 2003 and 2004, respectively. At our hospital, 4 cycles of MVAC and cisplatin/gemcitabine have a similar cost of $42,776 and $41,936, respectively. The model cost of $43,000 assumed additional cost of physician reimbursement during hospitalization. Due to variations in geographic reimbursement for procedures as well as to account for different practice patterns and complications, we performed sensitivity analyses with a wide range of values to determine the effect on cost-effectiveness of screening. This range of values is shown in Table 1.

Costs for Different Stages

All patients with cancer underwent an initial evaluation with office cystoscopy and cytology as well as a physician visit and an intravenous pyelogram (IVP). Those patients in the screening group had the additional cost of a marker. Each patient, regardless of stage, also had the cost of initial TURBT. Additional costs over the 5-year period depended on stage of disease. Although we recognize that there are variations in practice regarding follow-up protocols, we made assumptions utilizing our standard follow-up procedures. Using our sensitivity analyses, we varied costs per stage over a wide range to account for different practices (Table 1).

Superficial (AJCC T0, T1) Disease

We assumed that there would be routine follow-up with cystoscopy and cytology every 3 months in the first 2 years and then every 6 months in Years 2–5 and then yearly thereafter. The costs of these visits were included for each patient. We also added in the cost of an upper tract study (IVP) every 2 years. Patients with high-grade disease had the additional cost of BCG.

Muscle Invasive Disease

All patients with muscle-invasive (regional) disease underwent a cystectomy after initial evaluation and TURBT. Additional costs included physician visits, routine laboratory, chest radiograph, and follow-up computed tomography (CT) of the abdomen and pelvis.

Metastatic Disease

All patients with metastatic disease underwent chemotherapy after initial evaluation and TURBT. Additional costs included physician visits, routine laboratory, chest radiograph, and follow-up CT scans of the abdomen and pelvis. We also added an additional cost of living with metastatic disease that we varied within our sensitivity analyses (Table 1).

Outcomes

There were 2 primary outcome measures including cost and survival for both the screening and standard groups. One-way and 2-way sensitivity analyses were performed varying the costs of treatment for different stage cancers, cancer incidence, marker variable (cost, sensitivity, and specificity), and risk reduction from screening. Two-way sensitivity analyses compared the screening and standard strategies based on best cost-effectiveness (cost divided by life-years saved).

An additional analysis was performed to adjust the interval of screening patients. In our base analysis, we assumed a 1-time screen at the initiation of the study. To our knowledge, there are no data in the literature regarding the incidence rates of bladder cancer for high-risk patients after an initial screening. We performed analyses evaluating yearly and every other year screening assuming an initial incidence of 4% followed by a low incidence of 0.1%, which approximates the cancer incidence for bladder cancer in Surveillance, Epidemiology, and End Results (SEER) data.[5]

RESULTS

Screening for bladder cancer in a population with an annual 4% incidence of bladder cancer resulted in a gain of 3.0 life-years per 1000 subjects at a cost savings of $101,000 for the population assuming a 50% downstaging in the screened population from muscle-invasive to nonmuscle-invasive disease. Adjusting for other cause mortality did not vary the results significantly. Even with a 3.5% yearly death rate from other causes, as seen in men in their early 70s, a screened group gains 2.9 life-years at a cost savings of $100,000. The cancer incidence had the greatest impact on the cost-effectiveness of screening. At a 2% annual cancer incidence, screening resulted in a gain of 1.48 life-years per 1000 subjects at a saving of $16,000. An annual incidence of 1%, however, only resulted in a gain of 0.7 life-years at a cost of $35,358 per life-year saved.

One-Way Sensitivity Analyses

One-way sensitivity analyses were performed to identify the threshold where screening and standard identification of bladder cancer were equally cost-effective (Table 1). Screening is the most cost-effective strategy as long as cancer incidence is greater than 1.6%, tumor marker costs <$126, marker sensitivity is >26%, marker specificity is >54%, downstaging with screening is >20%, and office cystoscopy costs <$694.
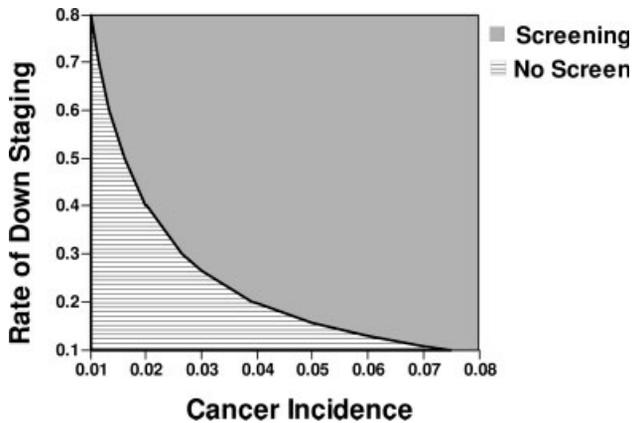
FIGURE 1. Two-way sensitivity analysis. The impact of varying the annual incidence of cancer and the risk reduction on the cost-effectiveness of different detection strategies. Shaded regions (labeled screening) represent scenarios in which screening is more cost-effective than not screening.

FIGURE 2. Two-way sensitivity analysis. The impact of varying the annual incidence of cancer and the marker cost on the cost-effectiveness of different detection strategies. Shaded regions (labeled screening) represent scenarios in which screening is more cost-effective than not screening.

FIGURE 3. Two-way sensitivity analysis. The impact of varying marker sensitivity and specificity on the cost-effectiveness of different detection strategies at a fixed cost of $24. Shaded regions (labeled screening) represent scenarios in which screening is more cost-effective than not screening.

Varying the costs of cystectomy, TURBT, chemotherapy, end-of-life care, costs of metastatic disease, and CT scan over a wide range did not affect the superiority of screening. Rates of death from other causes between 0% and 20% per year also did not affect the superiority of screening.

Two-Way Sensitivity Analyses

We performed several 2-way sensitivity analyses to evaluate the effect of varying 2 variables over a range of values (Figs. 1–4). The incidence of cancer greatly influences both the risk reduction and cost required of a screening test for it to be cost-effective (Figs. 1, 2). The greater the possibility of downstaging bladder cancer, the lower the incidence of disease necessary for screening to be cost-effective (Fig. 1). At a 1% incidence, a marker would need to result in a downstaging of 80% to remain cost-effective, but with an incidence of 4%; screening is cost-effective if downstaging is greater than 20%. Likewise, a higher incidence of disease will allow for a higher cost of tumor marker (Fig. 2). At a 1% cancer incidence, a marker costing $24 has a discounted cost per life-year saved of $34,841, but a marker can cost up to $200 if the incidence is over 6%, assuming equivalent sensitivity and specificity. The marker specificity and sensitivity have a significant impact on the cost-effectiveness of screening (Fig. 3). A lower specificity results in more false-positive findings and resultant increase in evaluations. At a 4% cancer incidence, a tumor marker specificity of 86% yields a discounted cost per life-year savings of $101,000, but a decrease of specificity to 50% results in a discounted cost per life-year saved of $4,384 and a specificity of 30% increases costs to $25,599 per life-year saved. The more expensive a marker utilized, the higher the speci-
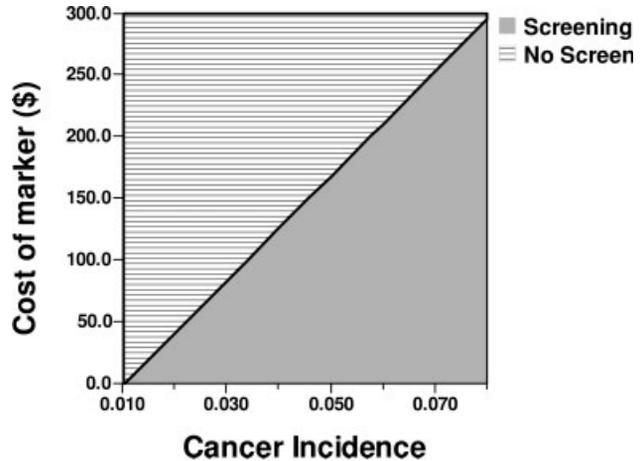
ficity required for the marker to be cost-effective (Fig. 4). The additional cost of the marker must be balanced by fewer false-positive results and less cost for unnecessary workups.

Varying Interval of Screening

In our base model, we evaluated a 1-time screen of the patient group due to lack of data regarding yearly incidence rates of cancer in high-risk patients with a negative prior screen. However, we modified our model to allow for both annual and biannual screening assuming a cancer incidence of 0.1%, which is similar to SEER rates. If a population is screened annually with

FIGURE 4. Two-way sensitivity analysis. The impact of varying marker cost and specificity on the cost-effectiveness of different detection strategies. Shaded regions (labeled screening) represent scenarios in which screening is more cost-effective than not screening.
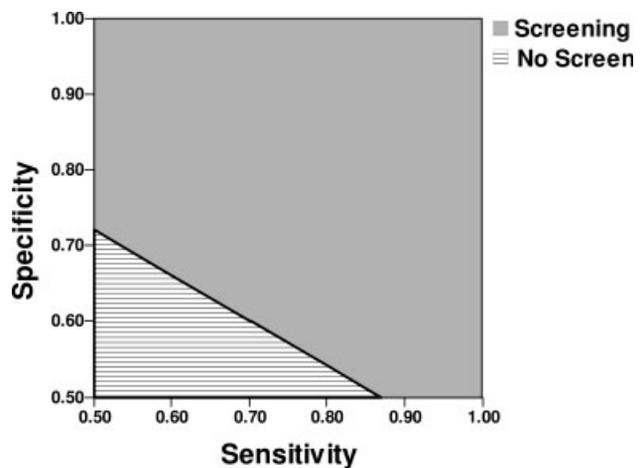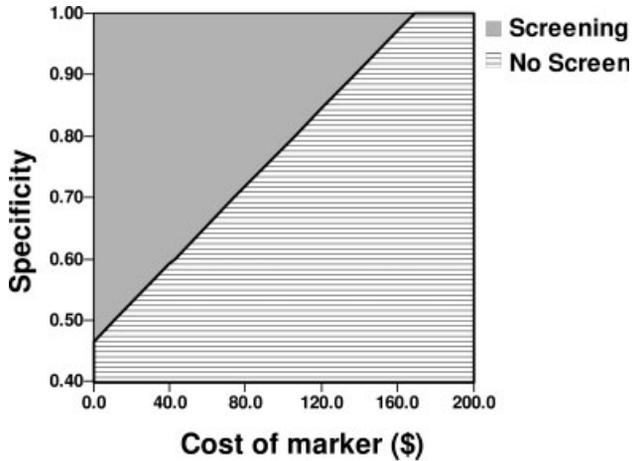
an initial cancer incidence of 4% and subsequent yearly incidence of 0.1%, the discounted cost per life-year saved is $46,693. For such a strategy to be cost-effective the initial cancer incidence would have to be > 7%. If a population is screened biannually with an initial cancer incidence of 4% and subsequent yearly incidence of 0.1%, the discounted cost per life-year saved is $6,837. Because there are very few additional cancers detected, the incremental discounted life-year gain is <0.1 years with either of these strategies.

Cystoscopy and Cytology as Screening Tools

If one were to use cystoscopy and cytology in all patients as the screening tool for bladder cancer without an IVP assuming a 95% sensitivity and specificity, there would be a 3.6 discounted life-year survival advantage at a cost of $30,387 per life-year saved with a cancer incidence of 4%. A cancer incidence of only 1% will result in a cost per life-year saved of $291,000.

DISCUSSION

Bladder cancer is an ideal disease for screening in a high-risk population. The risk factors for bladder cancer are well known, including smoking and environmental/occupational toxins such as petroleum products and aniline dyes.[1] The disease has a high prevalence and >25% of patients present at an advanced stage.[4] Survival is significantly improved in patients with nonmuscle-invasive cancer.[4] The main limitations to broad use of screening have been the identification of accurate and cost-effective markers for disease presence and targeting an appropriate population. With the approval of BladderChek (NMP22) testing by the FDA for high-risk

TABLE 3
Cost Per Life-Years Saved for Cancer

Disease	Cost per life-year saved ($)
Prostate cancer (prostate-specific antigen and digital rectal examination)[27]	2300–5000
Colon cancer (colonoscopy)[28,29]	10,000–40,000
Breast cancer (mammography)[30]	16,000–18,800*
Breast cancer (mammography)[31]	48,000–89,000†
Cervical cancer[32]	£36,000

* Marginal cost life-year saved.
† Marginal cost quality life-year saved.

patients, one has an initial test that can be assessed for efficacy in screening.

A recent evaluation of the cost per cancer-detected found that the use of BladderChek (NMP22) would be in the $2000 to $5000 range if used in a high-risk population but would be >$100,000 if used in the overall population.[22] In that analysis, the cost per cancer detected in the high-risk population was similar or superior to screening for prostate, breast, and colon cancer. The current analysis found that in a population with a >1.6% cancer incidence, screening with BladderChek would result in both improved overall survival and a cost savings. This is a unique finding because most evaluations of screening policies for other cancers such as prostate, breast, colon, and cervical found a cost per life-years saved of up to $50,000 (Table 3). Despite the low overall bladder cancer incidence utilized in the model, downstaging as a result of screening rendered a discounted life savings of 3 life-years over a 5-year period.

The conclusions of this analysis are strengthened by the results of additional analyses that relaxed various model assumptions. Our model found that screening is more cost-effective than not screening as long as the cancer incidence is >1.6%, tumor marker costs are <$126, marker sensitivity is >26%, marker specificity is >54%, downstaging with screening is >20%, and office cystoscopy costs <$694. Although there is geographic variation in Medicare reimbursement and costs vary by hospital and institution, our analysis evaluated a wide range of values for TURBT, cystectomy, chemotherapy, end-of-life care, costs of metastatic disease, and radiologic tests (CT/IVP) and found no impact on the advantage of bladder cancer screening. In addition, taking into account other-cause mortality did not change the overall life-savings if screening was performed in 50-year-old subjects or 70-year-old subjects.

There are several reasons bladder cancer screening was a superior strategy in terms of both survival and cost. First, there is a survival benefit to earlier

cancer detection from muscle-invasive disease to non-muscle-invasive disease even if only a small proportion of subjects develop cancer. We assumed that our population would have a 4% cancer incidence. This is a reasonable assumption if one targets high-risk patients. Grossman et al.[10] found a 6% cancer incidence in patients who are at high risk or symptomatic. Because we are limiting our screening population to asymptomatic high-risk patients, this rate is likely to be lower, leading to our baseline assumption of 4% incidence. The cost-advantage of $101,000 for 1000 screened subjects comes from the significant costs associated with muscle-invasive and metastatic bladder cancer. Even patients with organ-confined disease have a high risk of progression and death from bladder cancer.[11,12] Costs of chemotherapy and cystectomy far outweigh the costs associated with repeat TURBT and intravesical therapy. Another advantage for bladder cancer screening is the low cost of BladderChek ($24), such that most patients without cancer do not have a high cost burden as compared with screening using colonoscopy or mammography. Even those with false-positive testing only have the additional cost of cystoscopy and cytology and physician visit ($317). As long as cystoscopy costs were <$694, screening was less costly than no screening.

The potential for downstaging and decreased mortality with bladder cancer screening has been demonstrated using hemoglobin dipstick testing.[6] Messing et al.[6] found a 4.8% incidence of muscle-invasive disease and a 0% mortality at 2 years compared with a 23.9% incidence of muscle-invasive disease with 16% cancer-specific mortality in a screened and nonscreened population, respectively.[6] We recognize that our model hinges on the assumption that bladder cancers can be detected before muscle invasion. Although the study by Messing et al.[6] found an 80% downstaging among 1500 asymptomatic men screened with hemoglobin dipstick, we assumed only a 50% downstaging but evaluated the model over a wide range of values. Our model found that even a 20% downstaging favored a strategy of screening for bladder cancer. Because many high-grade cancers are identified before muscle invasion, it is not unreasonable to believe that a screening strategy could detect these cancers.[14,23]

The advantage of BladderChek and other recently developed urine-based markers is the increase in sensitivity, specificity, and PPV compared with hemoglobin dipstick.[9,10] This allows improved detection of cancer and fewer unnecessary work-ups. Data from studies examining NMP22 for patients without a history of bladder cancer reveal a PPV of 19.7% to 29%.[10,24] This is comparable to a 25% to 33% PPV afforded by a transrectal ultrasound-guided (TRUS) biopsy for a prostate-specific antigen (PSA) >4 ng/mL.[25] In their prospective trial evaluating the use of NMP22 in patients with risk factors for bladder cancer, Grossman et al.[10] reported an improvement in the PPV of the NMP22 test from 19.7% to 37% when including only those patients at highest risk (men age >60 years with a history of smoking). Ponsky et al.[26] found an improvement in the specificity of NMP22 from 84% to 99% by excluding patients with benign inflammatory or infectious conditions, calculi, stents, nephrostomy tubes, bowel interposition, and recent genitourinary instrumentation. A disadvantage of a low PPV is a high number of unnecessary workups with resultant cost, patient morbidity, and anxiety. In our analysis, for every 1000 subjects there is an additional cost of $44,000 accrued due to false-positive tests. Fortunately, cystoscopy and cytology have a minimal morbidity and have a high specificity and sensitivity. As such, complications are rare and even patients with false-positive results can have a quick examination that can alleviate their anxiety. Used alone as a screening tool, cystoscopy and cytology were found to be more costly without a significant increase in overall survival compared with BladderChek.

The question of frequency of screening is important but difficult to assess. Our model is limited by the available literature, which does not include studies evaluating the cancer incidence in patients previously screened for bladder cancer. We modeled a scenario in which the initial screen has a 4% incidence but subsequent annual incidence of cancer is 0.1%, which is similar to SEER incidence rates. Using yearly screening will significantly increase the cost per discounted life-year without improving overall survival. Biannual screening reduces this cost but future studies will be necessary to provide more information on actual cancer incidence in men who are screened for bladder cancer.

There are several limitations with this analysis. To our knowledge there are no randomized trials comparing survival with and without a screening strategy for bladder cancer. To counter this problem, we used a Markov model and an analysis of the literature to estimate survival with and without screening. We recognize that the incidence of cancer in asymptomatic patients may not be as high as 4% to 6% and performed various analyses evaluating a range of incidence rates. A population with over a 1.6% cancer incidence is ideal for screening and a prospective study stratifying patients by age, smoking history, and occupational exposures will be required to identify an appropriate subset of patients. The costs utilized for managing superficial, muscle-invasive, and metastatic disease will likely vary by institution and health care environment, but the conclusions of this analysis did not change despite >100% variance in these values. Furthermore, this

analysis addressed cause-specific survival and costs but did not consider quality-of-life issues. Certainly those patients in the screening group who could avoid cystectomy probably benefit from both improved survival and better quality of life. However, the anxiety associated with a false-positive diagnosis will lessen the quality of life of patients in the screening groups. Future studies will be necessary to assess the impact of screening on quality of life of these patients. We also assumed that patients with a false-negative screen will present to their physicians when their cancers become symptomatic. It is difficult to speculate whether these patients may delay their care if they have the false assumption that they are cancer-free. In our base model, we assumed that all patients with cancer will be diagnosed in the first year. We did not include a lead-time bias. We recognize that this biases for the screening group because some patients will die of other causes before diagnosis of bladder cancer. However, unlike prostate and kidney cancer, bladder cancer is rarely discovered at autopsy and, thus, most cancers will become symptomatic and there is a low likelihood to find a "clinically insignificant" bladder cancer. Although we specifically evaluated BladderChek, our model can be used to evaluate the cost-effectiveness of any marker using its cost, sensitivity, and specificity. We also utilized performance characteristics (sensitivity and specificity) from the literature, but performance characteristics for small tumors may be significantly different. Future studies will need to evaluate the effect of tumor size on screening, but our sensitivity analyses demonstrate that even a significant drop in sensitivity and specificity will allow bladder cancer screening to be cost-effective. Future markers will likely be developed that may improve specificity or sensitivity and one can determine what cost would result in their being cost-effective for screening.

Conclusions

The decision to implement a screening program depends on multiple factors including survival benefits, cost, and accurate, noninvasive tests for the disease. Bladder cancer, with an estimated >63,210 cases and 13,180 deaths for 2005, may be an ideal disease for screening in a high-risk population.[2] We found that a urine-based marker such as NMP22 can reduce mortality and save costs in a high-risk population. Prospective randomized trials testing the accuracy of bladder cancer detection in a completely asymptomatic cohort and evaluation of outcomes regarding cancer-specific mortality are indicated before a bladder cancer screening policy can be determined.

REFERENCES

1. Silverman DT, Hartge P, Morrison AS, Devesa SS. Epidemiology of bladder cancer. *Hematol Oncol Clin North Am.* 1992;6:1–30.
2. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. *CA Cancer J Clin.* 2005;55:10–30.
3. Botteman MF, Pashos CL, Redaelli A, Laskin B, Hauser R. The health economics of bladder cancer: a comprehensive review of the published literature. *Pharmacoeconomics.* 2003; 21:1315–1330.
4. American College of Surgeons. Commission on Cancer National Cancer Database. Available at URL: http://www.facs.org/cancer/ncdb/index.html Accessed on September 7, 2005.
5. Surveillance, Epidemiology, and End Results (SEER) Program (available at URL: www.seer.cancer.gov) SEER*Stat Database: Incidence — SEER 9 Regs Public-Use, Nov 2004 Sub (1973–2002), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2005, based on the November 2004 submission.
6. 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.
7. Messing EM, Vaillancourt A. Hematuria screening for bladder cancer. *J Occup Med.* 1990;32:838–845.
8. Britton JP, Dowell AC, Whelan P, Harris CM. A community study of bladder cancer screening by the detection of occult urinary bleeding. *J Urol.* 1992;148:788–790.
9. Lotan Y, Roehrborn CG. Sensitivity and specificity of commonly available bladder tumor markers versus cytology: results of a comprehensive literature review and meta-analyses. *Urology.* 2003;61:109–118.
10. Grossman HB, Messing E, Soloway M, et al. Detection of bladder cancer using a point-of-care proteomic assay. *JAMA.* 2005;293:810–816.
11. Lotan Y, Gupta A, Shariat SF, et al. Lymphovascular invasion is independently associated with overall survival, cause-specific survival, and local and distant recurrence in patients with negative lymph nodes at radical cystectomy. *J Clin Oncol.* 2005;23:6533–6539.
12. Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol.* 2001;19:666–675.
13. Heney NM, Ahmed S, Flanagan MJ, et al. Superficial bladder cancer: progression and recurrence. *J Urol.* 1983;130:1083–1086.
14. Millan-Rodriguez F, Chechile-Toniolo G, Salvador-Bayarri J, Palou J, Vicente-Rodriguez J. Multivariate analysis of the prognostic factors of primary superficial bladder cancer. *J Urol.* 2000;163:73–78.
15. Kurth KH, Denis L, Bouffioux C, et al. Factors affecting recurrence and progression in superficial bladder tumours. *Eur J Cancer.* 1995;31A:1840–1846.
16. Kiemeney LA, Witjes JA, Verbeek AL, Heijbroek RP, Debruyne FM. The clinical epidemiology of superficial bladder cancer. Dutch South-East Cooperative Urological Group. *Br J Cancer.* 1993;67:806–812.
17. Yan Y, Andriole GL, Humphrey PA, Kibel AS. Patterns of multiple recurrences of superficial (Ta/T1) transitional cell carcinoma of bladder and effects of clinicopathologic and biochemical factors. *Cancer.* 2002;95:1239–1246.
18. Haukaas S, Daehlin L, Maartmann-Moe H, Ulvik NM. The long-term outcome in patients with superficial transitional cell carcinoma of the bladder: a single-institutional experience. *BJU Int.* 1999;83:957–963.

19. von der Maase H, Hansen SW, Roberts JT, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol.* 2000;18:3068–3077.

20. National Center for Health Statistics. Available at URL: http://www.cdc.gov/nchs/deaths.htm Accessed on September 25, 2005.

21. Gold MR, Siegel JE, Russell LB, et al. *Cost-Effectiveness in Health and Medicine.* New York: Oxford University Press; Year.

22. Svatek RS, Sagalowsky AI, Lotan Y. Economic impact of screening for bladder cancer using bladder tumor markers: a decision analysis. *J Urol Oncol.* 2006;24:338–343.

23. Herr HW, Schwalb DM, Zhang ZF, et al. Intravesical bacillus Calmette-Guerin therapy prevents tumor progression and death from superficial bladder cancer: ten-year follow-up of a prospective randomized trial. *J Clin Oncol.* 1995;13:1404–1408.

24. Zippe C, Pandrangi L, Potts JM, Kursh E, Novick A, Agarwal A. NMP22: a sensitive, cost-effective test in patients at risk for bladder cancer. *Anticancer Res.* 1999;19:2621–2623.

25. Murphy AM, McKiernan JM, Olsson CA. Controversies in prostate cancer screening. *J Urol.* 2004;172:1822–1824.

26. 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.

27. Benoit RM, Gronberg H, Naslund MJ. A quantitative analysis of the costs and benefits of prostate cancer screening. *Prostate Cancer Prostatic Dis.* 2001;4:138–145.

28. Pignone M, Rich M, Teutsch SM, Berg AO, Lohr KN. Screening for colorectal cancer in adults at average risk: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2002;137:132–141.

29. Redaelli A, Cranor CW, Okano GJ, Reese PR. Screening, prevention and socioeconomic costs associated with the treatment of colorectal cancer. *Pharmacoeconomics.* 2003; 21:1213–1238.

30. Rosenquist CJ, Lindfors KK. Screening mammography beginning at age 40 years: a reappraisal of cost-effectiveness. *Cancer.* 1998;82:2235–2240.

31. Shen Y, Parmigiani G. A model-based comparison of breast cancer screening strategies: mammograms and clinical breast examinations. *Cancer Epidemiol Biomarkers Prev.* 2005;14: 529–532.

32. Peto J, Gilham C, Fletcher O, Matthews FE. The cervical cancer epidemic that screening has prevented in the UK. *Lancet.* 2004;364:249–256.