Screening for Bladder Cancer using the urinalysis/dipstick method

A report for the National Screening Committee

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Introduction

This report is a partial update of a previous NSC evaluation of screening for bladder cancer (Laitner 2002) and is best read in conjunction with that report. It concluded that urine dipstick testing for small quantities of blood in asymptomatic individuals, microscopic haematuria (MH) did not satisfy the NSC criterion that there should be a simple, safe, precise and validated screening test for any proposed screening programme:

> The positive predictive value of MH is low and may not confer a significantly higher risk for bladder cancer than a negative result for MH. For this reason MH is not considered a valid test for bladder cancer in the context of population screening (Laitner 2002).

In recent years a number of novel urine-based bladder tumour markers (UBBTMs) have been developed (Shirodkar & Lokeshwar 2008). This update assesses the extent to which urine dipstick testing or any of the newer UBBTMs have been shown to offer a simple, safe, precise and validated screening test for bladder cancer in apparently healthy people (NSC criterion number 5). It does not address the question of whether early treatment, for patients identified through screening, leads to better outcomes than late treatment (NSC criterion number 10), because it would be premature to re-appraise a potential bladder cancer screening programme against the other NSC criteria until a suitable screening test has been validated.

This update is based on a literature search undertaken by Imperial College, London. The details of the search strategy are attached as Appendix 1.

Defining the population that is relevant to the NSC

The NSC defines screening as 'a process of identifying apparently healthy people who may be at increased risk of a disease or condition'. In the context of screening for bladder cancer, this review defines 'apparently healthy people' as those who do not have any urinary symptoms, such as visible blood in the urine (macroscopic haematuria) or discomfort associated with urination (dysuria), and who have no previous history of bladder cancer. The population of apparently healthy people who could be invited for screening could be defined in terms of age, sex, or known risk factors such as smoking or occupational exposure to chemicals known to cause bladder cancer.

Investigation of individuals with symptoms or with a history of bladder cancer is beyond the scope of this paper and is unaffected by any of its conclusions.

Type of bladder cancer that is most relevant to screening

The most common type of bladder cancer in the UK is transitional cell cancer, of which there are two distinct types. One is a low-grade papillary tumour that frequently recurs, but only 10-20% progress to invasion of the bladder wall. The second is a high grade malignancy which can present as dysplasia or carcinoma in situ, but which frequently presents as invasive disease. Patients with invasive tumours are at high risk for disease progression, and despite definitive therapy (frequently cystectomy), the overall 5-year mortality rate is usually reported to be in the range of 40-60% (Jakse et al 2004:10).

For a bladder cancer screening programme to be effective in reducing mortality, any screening test must be able to detect cancers that are destined to become muscle-invading, but before they have done so (Madeb & Messing 2008). Therefore the ideal screening

tool(s) for BC would have excellent sensitivity for high-grade cancer, and good sensitivity for lower grade cancer, so that missed tumours would not undermine the confidence of physicians and participants in the screening endeavour (Madeb & Messing 2007). This does not imply that the screening tool need necessarily discriminate between higher and lower grade tumours in routine use, merely that its sensitivity for high- and low-grade tumours should be established from research studies. The ideal screening tool(s) would also have high sensitivity for small tumours.

General observations regarding the performance of UBBTMs

Messing (2007) observed that the reported sensitivities and specificities of all UBBTMs vary considerably, depending on the application and from study to study. Van Rhijn (2009) collated data on the performance of several UBBTMs for patients under surveillance for recurrent bladder cancer, disaggregating the data according to tumour grade (Table 1), where G3 is the highest grade. Although these data were not obtained from studies of apparently healthy people, they do show that all the UBBTMs included have the desirable property of being more sensitive for higher grade tumours. The authors did not report how sensitivity varies in relation to tumour size, but Madeb & Messing (2007) state that 'of concern is that, for almost all available markers that have been elucidated, the size of the tumour greatly affects sensitivity. Smaller tumours (the ones that would, optimally, be detected in screening) even high-grade ones, have false-negative results far more often than larger ones'.

Table 1: performance of UBBTMs in surveillance for recurrent bladder cancer

Marker (number of studies)	Sensitivity (number of patients)			Specificity (no. patients)
	G1	G2	G3	
BTA stat (7)	45 (228)	60 (206)	75 (208)	79 (972)
NMP22 Elisa (4)	43 (111)	58 (139)	82 (144)	64 (357)
NMP22 BladderChek (1)	32 (38)	44 (16)	75 (32)	87 (565)
uCyt + /ImmunoCyt (3)	79 (172)	86 (108)	90 (113)	72 (1509)
FISH UroVysion (3)	38 (52)	51 (28)	82 (38)	75 (169)
Microsatellite (6)	61 (69)	63 (53)	92 (40)	77 (869)
Cytology (10)	17 (239)	34 (274)	58 (201)	95 (861)

Studies of UBBTMs in populations relevant to the NSC

Based on a literature search conducted in January 2009, supplemented by requests to authors of relevant studies for any more recent publications, this review identified eight studies of UBBTMs in populations relevant to the NSC (Table 2). Several other publications (for example, Grossman et al 2005, Lotan et al 2008, Sarosdy et al 2006) present results in which data from patients with symptoms are aggregated with data from populations relevant to the NSC, and therefore could not be used for this review.

Table 2 summarises key features and results of the eight identified published studies of screening for bladder cancer in populations relevant to the NSC. With the exception of the study by Schmitz-Drager et al (2008) only screen-positive patients were investigated by cystoscopy and imaging. So it is possible that some cancers remained undiagnosed and therefore, strictly speaking, sensitivity and specificity cannot be calculated. The 'maximum

sensitivity' estimates shown in Table 2 are calculated on the assumption that full investigation of all screen-negative individuals would have revealed no further cancers. Although this may not be true, the estimates do serve to illustrate the limited sensitivity, in a population screening context, of the tests that have been evaluated.

Screening strategies that begin with urine dipstick testing for haematuria

The two older studies of urine dipstick testing for haematuria (Messing et al 1992 and Messing et al 2006; Britton et al 1992 and Mayfield & Whelan 1998) probably achieved good sensitivity, but each participant was required to complete many dipstick tests. Hedelin et al (2006) report the results of a study in which men aged 60-70 yrs underwent a single screen with urine dipstick testing for haematuria. Urine samples of those who were screen-positive for haematuria, and of alternate patients who were screen-negative for haematuria, were also tested for UBC (a novel UBBTM); since the results for these two groups of patients were combined, a proper assessment of the test characteristics of UBC is not possible. Nearly 24% of men tested positive for haematuria 1+, and 10% for haematuria 2+. Roobol et al (2009) report early results of a study in which men aged 50-75 yrs undergo daily urine dipstick testing for 14 days. Men with at least one sample positive for haematuria are tested for four UBBTMs (NMP22, microsatellite analysis, FGFR3 mutation snapshot and methylation MLPA test), and those with one or more positive results are offered cystoscopy. Data on sensitivity and specificity are not yet available but, as in the older studies of urine dipstick testing for haematuria, a large proportion of participants (24.8%) tested positive for haematuria, which raises questions about the feasibility of this approach for population screening. Svatek and Lotan (2008) described briefly a study being carried out by the M.D.Anderson Specialised Programmes of Research Excellence in which participants will undergo multiple dipstick testing for haematuria, and everyone with a positive test will undergo cystoscopy and three marker tests (the NMP22 BladderChek test, UroVysion, and Immunocyt); no results from this study had been published at the time of writing.

Although the immunocytological test uCyt+ achieved 80% sensitivity in the study by Schmitz-Drager et al (2008), participants were selected on the basis of having microhaematuria as an incidental finding in routine care. Hemstreet et al (2001) found that a single urine dipstick test for haematuria, even when repeated at intervals of 6-36 months for up to six years, achieved a maximum sensitivity of only 24%. This implies that a population screening programme which limited uCyt+ testing to those who were screen-positive on a single urine dipstick test for haematuria would have poor sensitivity overall.

Other screening strategies

The remaining four studies did not begin with urine dipstick testing for haematuria, but selected participants on the basis of age, gender, smoking history or occupational exposure to bladder carcinogens. Three of these studies (Lotan et al 2009, Marsh and Cassidy 2003, Steiner et al 2008) identified six cancers or less, so all the test performance characteristics are based on small numbers and will have wide confidence intervals. The study by Hemstreet et al (2001) detected 30 cancers, allowing more precision in estimating the performance of the tests. The only test that achieved more than 60% sensitivity was DNA 5CER (a DNA ploidy test), but this came at the cost of relatively poor specificity (86.5%), so that even in this moderately high-risk group the predictive value of a positive DNA 5CER test was only 5.5%.

Conclusion

No test or combination of tests for bladder cancer has yet been shown to be simple, safe, precise and validated in the context of population screening. Urine dipstick testing for

haematuria can offer reasonable sensitivity, but only if many repeat specimens are obtained, and only at the cost of many false positives. Few cancers have been detected in published studies of the performance of the newer UBBTMs in populations that are relevant to the NSC, but the limited data available suggests that none of them achieve an acceptable trade-off between sensitivity and specificity.

The Royal College of Physicians and the Association of Cancer Physicians have advised (in June 2010) that it would be valuable to support the association of parallel translational studies investigating diagnostic urinary biomarkers with current and future clinical trials, as a means of obtaining urine samples for molecular analysis. Their view is that ideally this should be done in a co-ordinated, centralised fashion (possibly via the NCRI bladder cancer Clinical Studies Group), to maximise the statistical value of specimens donated by patients.

Recommendation

NSC should not recommend screening for bladder cancer at this time, but should update this review when the results of the bladder cancer screening studies described by Svatek and Lotan (2008) Roobol et al (2009) become available.

Table 2: Studies of screening for bladder cancer in populations relevant to the NSC

Participants (reference)	Duration of screening intervention	Number of bladder cancers identified	Prevalence or incidence of diagnosed bladder cancer (per 1,000 people or person-years)	Test	Maximum sensitivity (%)	Specificity (%)	Percentage with a positive test	Positive predictive value (%)
1575 apparently healthy men aged ≥ 50 yrs (Messing et al 2006)	Two spells, 9 months apart, of 14 daily screens	21	13.3	Haematuria (up to 28 tests)	100	84.7	16.4	8.1
2356 apparently healthy men aged ≥ 60 yrs (Mayfield & Whelan 1998)	Weekly screen for 10 weeks	17	7.2	Haematuria (10 tests)	100	80.5	20.1	5.4
1096 apparently healthy men aged 60-70 yrs (Hedelin et al 2006)	Single screen	7	6.4	Haematuria ≥ 1+	71	76.4	23.9	1.9
				Haematuria ≥ 2+	57	90.1	10.2	3.6
395 apparently healthy men aged 50-75 yrs (Roobol et al 2009)	One spell of 14 daily screens	0	-	Haematuria (14 tests), then NMP22, microsatellite analysis, FGFR3 mutation snapshot and methylation MLPA test if haematuria +ve.	-	-	24.8	-
228 patients with microhaematuria as an incidental finding in routine care, no history of bladder cancer (Schmitz-Drager et al 2008)	Single screen	10	46	uCyt+/Immunocyt	80 (100 for 4 high grade cancers)	89	14	26
				cytology	40	97	5.1	36
183 participants considered high risk due ≥ 40 pack years of smoking (Steiner et al 2008)	Single screen	6	33	Haematuria	67	70.1	31.1	7.0
				FISH UroVysion	67	93.8	8.2	27
				NMP-22 BladderChek	17	94.4	6	9.1
				Cytology	17	94.9	5.5	10

Participants (reference)	Duration of screening intervention	Number of bladder cancers identified	Prevalence or incidence of diagnosed bladder cancer (per 1,000 people or person-years)	Test	Maximum sensitivity (%)	Specificity (%)	Percentage with a positive test	Positive predictive value (%)
1,502 people considered high risk due to age and smoking, or occupation (Lotan et al 2009)	Single screen	2	1.3	NMP-22 BladderChek			5.7	2.4
277 people with occupational exposure (Marsh and Cassidy 2003)	≤ 10 annual or semi-annual screens	3	0.2	Haematuria, cytology and quantitative fluorescence image analysis			4.5	4.6
2161 Chinese workers, most with occupational exposure to a bladder carcinogen (Hemstreet et al 2001)	≤ 6yrs, screening interval of 6-36 months	30	2.3	Haematuria	24	98.8	2.5	13.3
				Cytology	59	99.3	1.7	48
				DNA 5CER	68	86.5	17.2	5.5
				G-actin	5	80.7	23.1	0.3
				P300	57	97.9	3.2	25

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Appendix 1

Literature Search

Dr A Mackie
26th January 2009

Screening for Bladder cancer, using the dipstick/urinalysis method

Search undertaken by:

Emma Shaw
Principal Library Assistant
Chelsea and Westminster Campus

Database(s) Searched:

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)**: 1950 -present**

EMBASE (OvidSP)**: 1996 – 2009 week 03**

The Cochrane Library: 2001 - present

When conducting searches in more than one database, we use reference management software to identify and remove duplicate records between databases. This process is approximately 95% accurate and therefore you may find a small number of duplicate records in your search results.

Summary of Search:

Screening for Bladder cancer using the urinalysis/dipstick method
This is a broad search designed to pick up all aspects related to screening for bladder cancer combined with the concepts related to urinalysis and dipstick method of screening, and microscopic Hematuria.

Limits:

Years 2001 -
All Languages

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Search Strategy
Medline

	Searches	Results
1	(bladder adj3 cancer$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	16020
2	(bladder adj3 neoplasm$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	35402
3	(Bladder adj tum$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	7118
4	(Urinary adj tract adj malignanc$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	59
5	UTM.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	60
6	(transitional adj cell adj cancer$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	309
7	(transitional adj cancer adj cell$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	13

8	(transitional adj cell adj carcinoma$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	7541
9	TCC.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	2974
10	(papillary adj3 tum$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	2717
11	(urologic adj3 neoplasm$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	2432
12	Urologic Neoplasms/	2401
13	Urinary Bladder Neoplasms/	35332
14	Carcinoma, Transitional Cell/	13373
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	47406
16	Mass Screening/	60981
17	exp Diagnostic Tests, Routine/	4708
18	diagnostic techniques, urological/ or antibody-coated bacteria test, urinary/ or urinalysis/	3275
19	urine.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	154986
20	urinalysis.mp. [mp=title, original title, abstract, name of substance word, subject heading word]	6572
21	Urine/	29603
22	Reagent Strips/	2379
23	(Dipstick$ or (dip adj stick$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	1660
24	(Hematuria or haematuria).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	16273
25	Hematuria/	8988
26	strip$.mp.	38796
27	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	273443
28	27 and 15	5374
29	28	5374
30	limit 29 to yr="2001 - 2009"	1834*

Embase

	Searches	Results
1	(bladder adj3 cancer$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	12445
2	(bladder adj3 neoplasm$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	188
3	(Bladder adj tum$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	4049
4	(Urinary adj tract adj malignanc$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	25
5	UTM.mp.	28
6	(transitional adj cell adj cancer$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	150
7	(transitional adj cancer adj cell$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	9
8	(transitional adj cell adj carcinoma$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	5141
9	TCC.mp.	2026
10	(papillary adj3 tum$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	2057
11	(urologic adj3 neoplasm$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]	10
12	Bladder Tumor/	2017
13	Bladder Cancer/	9481
14	Papilloma/	1614
15	Transitional Cell Carcinoma/	4574
16	Bladder Carcinoma/	4978
17	Urinary Tract Cancer/	1064
18	Urinary Tract Carcinoma/	469
19	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	23776
20	Mass Screening/	6540
21	exp urinalysis/	28356
22	Urine/	3754
23	urine.mp. [mp=title, abstract, subject headings, heading word, drug trade	86249

	name, original title, device manufacturer, drug manufacturer name]	
24	**urinalysis.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]**	**26985**
25	**test strip/**	**526**
26	**strip$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]**	**16591**
27	**(Dipstick$ or (dip adj stick$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]**	**1032**
28	**(Hematuria or haematuria).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]**	**10065**
29	**Hematuria/**	**9062**
30	**microscopic hematuria/**	**7**
31	***"macroscopic hematuria"/**	**2**
32	**27 or 25 or 28 or 21 or 26 or 20 or 22 or 30 or 24 or 23 or 31 or 29**	**124328**
33	**32 and 19**	**3567**
34	**33**	**3567**
35	**limit 34 to yr="2001 - 2009"**	**2558***

The Cochrane Library

	Search	Hits
#1	bladder cancer:ti,ab.	120
#2	bladder neoplasm*:ti,ab	15
#3	bladder tum*:ti,ab	673
#4	"Urinary tract malignancy"	1
#5	"Urinary tract malignancies"	2
#6	UTM	1
#7	"transitional cell cancer"	10
#8	"transitional cancer cell"	0
#9	"transitional cancer cells"	0
#10	"transitional cell carcinoma"	205
#11	"transitional cell carcinomas"	8
#12	TCC	139
#13	"papillary tumor" OR "papillary tumour" OR "papillary tumors" OR "papillary tumours"	22
#14	"urologic neoplasm" OR "urologic neoplasms"	36
#15	MeSH descriptor **Urologic Neoplasms**, this term only	36
#16	MeSH descriptor **Urinary Bladder Neoplasms**, this term only	787
#17	MeSH descriptor **Carcinoma, Transitional Cell**, this term only	355

#18	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)	1293
#19	MeSH descriptor **Mass Screening**, this term only	3015
#20	MeSH descriptor **Diagnostic Tests, Routine** explode all trees	236
#21	MeSH descriptor **Diagnostic Techniques, Urological**, this term only	17
#22	MeSH descriptor **Antibody-Coated Bacteria Test, Urinary**, this term only	16
#23	MeSH descriptor **Urinalysis**, this term only	143
#24	urine:ti,ab	8821
#25	urinalysis:ti,ab	488
#26	MeSH descriptor **Urine**, this term only	514
#27	MeSH descriptor **Reagent Strips**, this term only	74
#28	Dipsticks* OR "dip stick"	24
#29	Hematuria or haematuria	501
#30	MeSH descriptor **Hematuria**, this term only	131
#31	(strip OR strips):ti,ab	801
#32	(#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31)	13843
#33	(#18 AND #32)	166
#34	(#33), from 2001 to 2009	90*

Results

The above search strategy retrieved 1834 citations from Medline. A similar search was conducted in Embase and The Cochrane Library. All citations were imported into a Reference Manager database, and duplicates removed.

Database	No. of citations retrieved	Exclusive
Medline	1834	1812
Embase	2558	1737
The Cochrane Library	89	51

TOTAL = 3,601