Gender inequalities in the promptness of diagnosis of bladder and renal cancer after symptomatic presentation: evidence from secondary analysis of an English primary care audit survey

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ABSTRACT

Objectives: To explore whether women experience greater delays in the diagnosis of bladder and renal cancer when first presenting to a general practitioner with symptoms caused by those cancers and potential reasons for such gender inequalities.

Design: Prospective national audit survey of cancer diagnosis.

Setting: English primary care (2009–2010).

Participants: 920 patients with bladder and 398 patients with renal cancer (252 (27%) and 165 (42%), respectively, were women).

Primary and secondary outcome measures: Proportion of patients with three or more pre-referral consultations; number of days from first presentation to referral; proportion of patients who presented with haematuria and proportion of patients investigated in primary care.

Results: Women required three or more prereferral consultations more often than men (27% (95% CI 21% to 33%) vs 11% (9% to 14%) for bladder (p<0.001); and 30% (22% to 39%) vs 18% (13% to 25%) for renal cancer (p=0.025)) and had a greater number of days from presentation to referral. In multivariable analysis (adjusting for age, haematuria status and use of primary care-led investigations), being a woman was independently associated with higher odds of three or more pre-referral consultations (OR=3.29 (2.06 to 5.25, p<0.001) for bladder cancer; and OR=1.90 (1.06 to 3.42, p=0.031) for renal cancer). Although presentation with haematuria was associated with more timely diagnosis of bladder cancer, gender inequalities did not vary by haematuria status for either cancer (p=0.18 for bladder and p=0.27 for renal). Each year in the UK, approximately 700 women with either bladder or renal cancer experience a delayed diagnosis because of their gender, of whom more than a quarter (197, or 28%) present with haematuria.

Conclusions: There are notable gender inequalities in the timeliness of diagnosis of urological cancers. There is a need to both reinforce existing guidelines on haematuria investigation and develop new

ARTICLE SUMMARY

Article focus
- Limited previous evidence suggests that women with urinary tract cancers may be diagnosed less promptly than men with the same cancers.
- Evidence is needed from contemporary clinical data sources to establish whether gender inequalities do exist, their magnitude, and their potential causes.

Key messages
- Women with bladder and renal cancer are more likely than men to require three or more prereferral consultations with a general practitioner, and to experience longer time intervals between presentation and hospital referral.
- There were gender differences for patients both with and without haematuria, suggesting that doctors often interpret the clinical importance of haematuria differently in men and women.
- Population health impact estimates suggest that gender inequalities can be reduced by reinforcing existing clinical guidelines on haematuria management. However, new approaches (such as use of clinical decision support tools) also need to be developed to improve the diagnosis of patients of either gender who present without haematuria.

Strengths and limitations of this study
- We were able to explore potential confounding of gender differences in diagnosis by gender differences in the management of haematuria or by differential use of primary care-led investigations.
- We have estimated the population health impact of the observed relative differences in the timeliness of diagnosis.
- The sample size of the study was relatively small (particularly for patients with renal cancer).

diagnostic decision aids and tests for patients who present without haematuria.

INTRODUCTION

Promptly diagnosing patients who present with symptoms caused by cancer is a pressing priority for healthcare systems worldwide.[1–5] Globally, most patients with cancer first present to a non-specialist doctor (usually a general practitioner), who has to appropriately suspect the diagnosis in order to instigate an onward referral to a specialist. Some diagnostic delays therefore occur after presentation to a general practitioner,[6] because signs and symptoms are initially attributed to a benign cause. Patients with certain sociodemographic characteristics may be at higher risk of experiencing a less prompt specialist referral.[7 8] Avoiding delays in diagnosis after presentation to a doctor is an important determinant of patient experience and matters greatly to all patients and their carers.[9–12]

In England, uniquely pronounced gender inequalities in relative survival from bladder cancer exist, with 5-year relative survival for men being 57%, compared with 44% for women.[13] Further, specifically for bladder and renal cancer (and using English patient-reported data), notable gender inequalities have been reported in the number of times patients had to see their general practitioner with cancer symptoms before referral to a specialist (table 1).[8] A US study also showed that women presenting with haematuria to a primary care physician are referred to a urologist for investigation less promptly than men.[14] Misattribution of symptoms of urinary tract cancers in women to benign urogenital causes (eg, urinary tract infection) has been hypothesised as the reason for these gender differences,[8] but several uncertainties remain: are gender differences in the number of pre-referral consultations apparent when using data sources other than patient surveys? Do differences in the number of prereferral consultations translate to differences in the time interval between first presentation and specialist referral? Could at least some of the gender differences in the promptness of diagnosis be explained by differences in presenting signs and symptoms (particularly haematuria)? Against this background, we set out to examine gender differences in the promptness of diagnosis of bladder and renal cancer.

METHODS

Data

We analysed data from the (English) National Audit of Cancer Diagnosis in Primary Care (2009–2010).[15] Data on different aspects of the diagnostic process were collected by general practitioners or other primary care professionals in an estimated total of 1170 general practices (~14% of all practices in England). Details of the methods used in the audit have been published previously.[15 16] Although general practice participation was voluntary, comparisons with cancer registration statistics indicate that the data set is representative of the age, sex and cancer type breakdown of patients with cancer in England.[15] Data were available on two interrelated measures of promptness of diagnosis,[16] that is, the number of prereferral consultations and the primary care interval (ie, the time interval between the first symptomatic presentation of a patient with cancer to a general practitioner and their first specialist referral for further investigation,[6] measured in days by subtracting the date of first hospital referral from the date of first presentation). We used a binary form of the number of prereferral consultations (three or more vs one or two consultations) reflecting the use of this outcome by both patient groups and UK policy-makers for purposes of public reporting of the performance of NHS hospitals.[17] Data were also available for patients' 5 year age group, sex, main presenting symptom and primary care investigations.

Analysis

Initial analysis was restricted to patients with at least one recorded general practitioner consultation before hospital referral and complete information on sex and age group.

In univariable analysis, we examined crude gender differences in promptness of diagnosis. We also described gender differences in haematuria status and in use of 'blood test' and ultrasound scan investigations (as these three factors have the potential to at least partially explain gender differences in promptness of diagnosis). Symptom analysis was restricted to macroscopic haematuria because it was the most common main presenting

Table 1 Gender differences in the promptness of diagnosis of urinary tract cancer (Cancer Patient Experience Survey, 2010)[8]

	Patients who saw their GP with cancer symptoms (N)	Patients with three or more GP consultations before hospital referral (n)	Patients with three or more GP consultations before hospital referral (n/N=%)	Crude odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Bladder					
Men	4254	624	14.7	Reference	Reference
Women	1295	357	27.6	2.29 (1.97 to 2.67)	2.33 (1.99 to 2.72)
Renal					
Men	391	103	26.3	Reference	Reference
Women	208	77	37.0	1.63 (1.12 to 2.36)	1.65 (1.13 to 2.40)

GP, general practitioner.

symptom, because of its singularly strong association with urological cancers[18–22] and because of the UK clinical guidelines by the National Institute of Health and Clinical Excellence (NICE) mandating urgent specialist referral of patients who present with macroscopic haematuria, independently of their gender ('male or female adult patients of any age who present with painless macroscopic haematuria should be referred urgently').[23] Hereafter, in this manuscript and tables, the term 'haematuria' will denote macroscopic haematuria. Investigations were restricted to 'blood test' (not otherwise specified in the data set) and ultrasound scan because they were the only two commonly recorded investigations (see online supplementary appendix 1).

Using multivariable logistic regression, we further explored the association between the number of prereferral consultations (three or more consultations vs one or two) and gender. First, we examined to what extent gender differences are confounded by other variables (age, haematuria status, ultrasound scan investigation, and 'blood test'). Subsequently, we used a final ('full') model including all variables. We further explored interactions of gender by all other variables. Because patients attend different practices, we used a sandwich estimator of standard errors.

Sensitivity analysis
We first repeated the multivariable regression model using different definitions of binary categories of the number of prereferral consultations (two or more vs one; and four or more vs one, two or three consultations). We further explored potential bias arising from missing data, using multiple imputation to produce a complete data set,[24–27] and repeated the multivariable analysis (outlined above). Multiple imputation assumes that data are 'missing at random' (MAR), that is, that any systematic differences between the missing and observed values can be estimated using information from the observed data. The imputation model included all variables used in the analysis model and, in addition, the primary care interval variable (as the primary care interval is strongly correlated with the proportion of three or more prereferral consultations[16]).

Population health impact
Assuming that the national audit data are generalisable to contemporary UK practice, we illustrate the potential

population health impact of the findings. For this estimation, we used a logistic regression model (three or more vs one or two consultations) including age, gender and haematuria status as covariates to predict the proportion of men and women (with and without haematuria) who require three or more prereferral consultations both in the presence and absence of gender differences. When assuming no gender differences, we replace the odds ratio for gender by 1. The obtained proportions are scaled using national incidence statistics to give annual numbers for the UK. Stata V.11 was used for all analyses, including the uses of *ice* and *mim* commands for multiple imputation.[28]

RESULTS
In total, there were 920 patients with bladder cancer and 398 patients with renal cancer, of whom 252 (27%) and 165 (42%), respectively, were women—proportions similar to contemporary UK population-based incidence statistics (28% and 38%, respectively, for bladder and renal cancer).[29] Unless where noted, after exclusion of patients whose diagnosis did not involve a prereferral consultation and missing data (see online supplementary appendix 2), complete case analysis was restricted to 740 patients with bladder cancer and 287 patients with renal cancer with at least one known prereferral consultation. Among patients with bladder and renal cancer, respectively, 91% and 85% were 55 years of age or older (ie, older than the age by which most women would have experienced their menopause) with no evidence of gender differences in these proportions (p=0.77 and p=0.76, respectively, for either cancer).

Univariable analysis
Women had longer primary care intervals compared with men for both cancers (table 2) and required three or more prereferral consultations more often than men for either bladder (27% vs 11%, p<0.001) or renal cancer (30% vs 18%, p=0.025, table 3). Although gender differences in the median primary care interval were relatively small (6 vs 4 days for bladder cancer and 16 vs 10 days for renal cancer), substantial differences existed in the tails of the distribution. For either bladder or renal cancer, the 75th centile in women was longer than that in men by about 2 weeks (table 2) and at the 90th centile, the difference increased to over 2 months

Table 2 Centiles of the primary care interval by gender for bladder and renal patients with cancer

| Centile | Bladder cancer (n=721) | | | Renal cancer (n=271) | | |
	Men (n=525) (days)	Women (n=196) (days)	p Value	Men (n=160) (days)	Women (n=111) (days)	p Value
25th	0	0	0.0059	0	3	0.016
50th	4	6		10	16	
75th	15	32.5		31	46	
90th	39	103		64	82	

Table 3 Univariable associations between gender and number of prereferral consultations, recorded haematuria, investigation by 'blood test' and ultrasound scan

| | Bladder cancer (n=740) | | | | | Renal cancer (n=287) | | | | |
| | Men (n=538) | | Women (n=202) | | | Men (n=169) | | Women (n=118) | | |
	n	Per cent	n	Per cent	p Value	n	Per cent	n	Per cent	p Value
Number of prereferral consultations										
1	320	59.5	102	50.5	<0.001	89	52.7	45	38.1	0.093
2	158	29.4	46	22.8		49	29.0	38	32.2	
3	40	7.4	23	11.4		17	10.1	16	13.6	
4	8	1.5	11	5.4		5	3.0	8	6.8	
5+	12	2.2	20	9.9		9	5.3	11	9.3	
1–2	478	88.8	148	73.3	<0.001	138	81.7	83	70.3	0.025
3+	60	11.2	54	26.7		31	18.3	35	29.7	
Haematuria										
Yes	394	73.2	143	70.8	0.51	57	33.7	23	19.5	0.008
No	144	26.8	59	29.2		112	66.3	95	80.5	
Ultrasound scan										
Yes	39	7.2	36	17.8	<0.001	44	26.0	35	29.7	0.50
No	499	92.8	166	82.2		125	74.0	83	70.3	
Blood test										
Yes	207	38.5	47	23.3	<0.001	71	42.0	45	38.1	0.510
No	331	61.5	155	76.7		98	58.0	73	61.0	

for bladder cancer and to about 3 weeks for renal cancer.

About two-thirds of all patients with bladder cancer and about one-quarter of all patients with renal cancer had haematuria as the main recorded primary symptom (table 3)—proportions similar to those previously reported in relevant patient populations (see online supplementary appendix 3).[18 19 21]

Multivariable analysis

Haematuria status was strongly related to having three or more prereferral consultations but explained only a small amount of the crude gender difference for either cancer (table 4 and online supplementary appendix 4). Similarly, there was no or a limited degree of confounding of the gender association by the other three variables (see online supplementary appendix 4). Using the full model, for bladder cancer, we find that three or more prereferral consultations were substantially more likely in women (OR=3.29 (2.06 to 5.25, p<0.001, table 4)) and less likely among those presenting with haematuria (OR=0.29 (0.19 to 0.46, p<0.001). For renal cancer, three or more prereferral consultations were more likely in women (OR=1.90 (1.06 to 3.42, p=0.031)) without evidence for an association with haematuria (p=0.25).

Regarding interactions, there was no evidence that gender differences in the proportion of patients with three or more prereferral consultations varied between patients with and without haematuria (p=0.18 for bladder and p=0.27 for renal cancer), as well as by age group (p=0.38 and p=0.10), 'blood test' use (p=0.71 and p=0.91) or ultrasound scan use (p=0.20 and p=0.59).

Sensitivity analysis

Repeating the multiple logistic regression using different binary categories of the number of prereferral consultations produced similar findings, particularly regarding associations with gender and haematuria status. Sensitivity analysis using multiple imputation of missing data also produced similar findings (see online supplementary appendices 5 and 6).

Population health impact

Each year in the UK, about 2900 women are diagnosed with bladder cancer and 3000 with renal cancer.[29] Of those women, we estimate that each year approximately 693 (~435 with bladder cancer and ~258 with renal cancer) experience three or more prereferral consultations when they would have required only one or two had gender inequalities not been present (see online supplementary appendix 7). More than a quarter (197, or 28%) of those women experience gender inequalities in the presence of haematuria.

DISCUSSION

In our study population, we found that women were more likely than men to experience a non-prompt diagnosis of bladder and renal cancer. Being a woman was an independent risk factor for a less timely diagnosis even after adjustment for age and presence/absence of haematuria or use of investigations. Moreover, differences in haematuria status between men and women explain only a small fraction of the crude gender differences. The findings indicate that generalists are less likely to suspect the diagnosis of urinary tract cancers in

Table 4 Crude associations and independent predictors of three or more prereferral consultations from the 'full' model (adjusted for gender, age, haematuria status and investigation status)

	Crude odds ratio	95% UCL	95% LCL	p Value*	Adjusted odds ratio	95% UCL	95% LCL	p Value*
Bladder (n=740)								
Men	Reference			<0.001	Reference			<0.001
Women	2.91	1.93	4.39		3.29	2.06	5.25	
16–54	1.52	0.75	3.10	0.23	1.20	0.53	2.72	0.34
55–64	0.68	0.34	1.37		0.59	0.29	1.21	
65–74	Reference				Reference			
75–84	1.32	0.79	2.19		1.18	0.69	2.03	
85+	1.42	0.75	2.66		1.27	0.65	2.49	
No haematuria	Reference			<0.001	Reference			<0.001
Haematuria	0.28	0.18	0.42		0.29	0.19	0.46	
No blood test	Reference			<0.001	Reference			<0.001
Blood test	2.09	1.39	3.13		2.47	1.58	3.86	
No ultrasound scan	Reference			<0.001	Reference			0.18
Ultrasound scan	2.59	1.50	4.45		1.55	0.82	2.93	
Renal (n=287)								
Men	Reference			0.026	Reference			0.031
Women	1.88	1.08	3.27		1.90	1.06	3.42	
16–54	1.17	0.49	2.76	0.99	1.05	0.41	2.74	0.99
55–64	1.04	0.49	2.22		0.85	0.39	1.85	
65–74	Reference				Reference			
75–84	0.95	0.42	2.13		0.95	0.38	2.38	
85+	1.23	0.45	3.36		0.97	0.34	2.77	
No haematuria	Reference			0.023	Reference			0.25
Haematuria	0.44	0.22	0.89		0.64	0.30	1.37	
No blood test	Reference			0.001	Reference			<0.001
Blood test	2.70	1.54	4.75		2.99	1.64	5.46	
No ultrasound scan	Reference			0.015	Reference			0.023
Ultrasound scan	2.06	1.15	3.69		2.17	1.11	4.24	

*From Wald tests, with joint tests used where applicable.
LCL, lower confidence limit; UCL, upper confidence limit.

women and that haematuria is often interpreted differently by general practitioners depending on the patient's gender. Optimising referral decisions for women with bladder and renal cancer who present with haematuria may have a notable impact on gender inequalities in promptness of diagnosis. However, many patients with urinary tract cancers (both women and men) present without haematuria. For those patients, new approaches are needed to help improve the promptness of diagnosis for patients of either gender.

Our findings amplify previous limited evidence on gender inequalities in the diagnosis of urinary tract cancers using patient-reported data in England and also previous US research.[8] [14] The strengths of the present study include the use of two different measures of promptness of diagnosis; the adjustment of the analysis for haematuria status and investigation use; the examination of potential interactions between gender and all other variables and the use of sensitivity analysis (including for missing data). Considering generalisability, the sample of patients was similar to population-based incidence data in respect of age, sex and cancer;[15] and to other primary care study populations in respect of the proportions of patients who presented with haematuria (see online

supplementary appendix 3).[18] [19] [21] Further, in supplementary analysis, we compared the characteristics of 535 participating with 2349 non-participating practices and found trivial differences in practice care quality and patient experience measures, and small differences for practice population and team size (see online supplementary appendix 8).

We believe that the principal reason for improving the timeliness of cancer diagnosis among symptomatic patients is to ensure as positive an experience of cancer care as possible for all patients,[9–12] although achieving such improvements may also help to improve treatment and prognosis for some. Indeed, there is some evidence indicating an association between delay and worse oncological outcomes for patients with bladder cancer presenting with haematuria.[30] [31] For bladder cancer in particular, women are more likely than men to be diagnosed at an advanced stage,[32] and there are also uniquely large gender inequalities in relative survival, as women have a substantially worse 5-year relative survival than men (57% vs 44%, respectively).[13] While the median primary care intervals for men and women with bladder cancer were similar (4 and 6 days, respectively), there were substantial differences in the tails of the

Table 5 Comparison of survey design and methodologies used by the National Audit of Cancer Diagnosis in Primary Care,[15] and the Cancer Patient Experience Survey 2010[8]

	National audit of cancer diagnosis in primary care	Cancer patient experience survey
Population	Patients with cancer in participating practices (about 14% of all English practices)	Patients with cancer across England
Sampling frame	Patients with new diagnosis of cancer during audited period (2009–2010)	Patients attending an NHS hospital for cancer treatment Jan–Mar 2010 (many of these cases have been diagnosed before the survey period)
Sample representativeness	Aimed to include all patients eligible for inclusion in the audit with minimal attrition (independently of survival length)	Only about two-thirds (67%) of all patients in the original sampling frame participated in the survey—after exclusion of people who had died, that is, patients with only short-term survival were likely to be a priori excluded
Method of outcome ascertainment	Case note review by general practitioner or other primary care professional (eg, practice nurse)	Patients responding to a specific survey question

NHS, National Health Service.

distributions that may have contributed to gender inequalities in stage and survival, although other factors such as gender differences in tumour subtypes or other biological factors may also be responsible.[33] These considerations however apply only to bladder cancer; we are not aware of evidence suggesting substantial gender differences in stage and survival from renal cancer.[13] The findings concord with and substantially amplify previous evidence from patient survey data indicating notable inequalities in the promptness of diagnosis of women with bladder and renal cancer (table 1).[8] The degree of concordance of the observed gender inequalities between national audit and patient-reported data is remarkable, given the differences in the methodologies used (see table 5).

The findings signal a large potential for improving the timeliness of diagnosis of urinary tract cancer in women. In part, this can be achieved by reinforcement and more rigorous adherence to existing clinical guidelines on investigation and management of haematuria.[23] Previous US research indicates that primary care physicians often do not adhere to guidelines for prompt investigation of patients presenting with haematuria.[34] Interventions to help general practitioners avoid initial misattribution of haematuria in women with urinary tract cancer to benign causes need to be promptly developed and evaluated. Elimination of gender differences in referral decisions in the presence of haematuria would only partially address overall gender inequalities, although it can help produce notable improvements with relative ease and speed. However, because many patients with urinary tract cancers present without haematuria, research to better understand these less specific presentations is also required. The implementation of clinical decision support tools (ideally combined with evaluation of their utility) may be helpful, since they incorporate information from multiple symptoms, signs and systemic manifestations (such as thrombocytosis).[20][35] The application

of consultation techniques, such as 'safety-netting', the development of new service models such as outreach facilities for specialist consultation with urologists and the development of new tests (eg, based on biomarkers) are also worthy of exploration and prioritisation of research investment. Improvements in the sensitivity of generalist consultations to suspect the presence of urological cancer among symptomatic patients should reduce gender inequalities, but should also benefit all patients of either gender. The positive predictive value of haematuria for urological cancer is generally lower than 15% (depending on age),[20] and is lower in women than men.[21] This means that even in a hypothetical situation where all patients presenting to general practitioners with haematuria as the main presenting symptom were referred promptly for specialist investigation, the great majority of them would be found not to have cancer. Nevertheless, clinical guidelines, such as those produced by NICE, mandate the referral of all patients who present with painless macroscopic haematuria independently of their gender–see also Methods.[23] Health economics analyses to explore the cost-effectiveness of these clinical protocols may be justified. These realisations can serve as potent reminders of the need for the development of newer tests (particularly easily accessible and acceptable point-of-care tests) and service models.

In conclusion, we report compelling evidence that in the study setting and during the study period women with urinary tract cancers were likely to experience a delayed diagnosis compared with men with the same cancers. Reinforcing existing guidelines on haematuria investigation and development of new diagnostic aids for patients who present without haematuria are needed. The findings should inform similar investigations in other country populations.

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