

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Lyratzopoulos, Georgios; Abel, Gary; McPHail, Sean; Neal, Richard; Rubin, Greg

VERSION 1 - REVIEW

REVIEWER	Willie Hamilton, University of Exeter Medical School
REVIEW RETURNED	17-Mar-2013

THE STUDY	The only 'no' related to the STROBE statement, which is fine. The English is excellent. The authors desperately try to avoid the word 'delay' - preferring the word non-prompt. At times this purism is taken too far [personally, i agree that the word delay has connotations of avoidability, which may not always be apposite - but in this paper, the whold throust of the non-promptness is that it MAY BE avoidable. Thus using the pejorative word 'delay' (which would read better) is probably acceptable/appropriate.
RESULTS & CONCLUSIONS	Yes; the paper by Shephard (which author RN and I am co-authors on) will be published in April, so this reference can be made 'normal' in any revision.
GENERAL COMMENTS	I wonder if the authors should address the clinical significance of these delays (see - I'm now using my preferred word!). It is only in the 'tail' of the distribution (the 90th centile) that women are as much as 2 months delayed. Are lesser durations important? it may also be worth mentioning the health economics of their (gentle) recommendations towards more rapid investigation of some women. Bladder cancer is expensive business: like colorectal, the costs of diagnosis may exceed the costs of treatment (as you have to investigate so many without cancer to find the cancers. With their recommendations (which i support clinically) just how many frogs will we have to kiss to find a prince?

REVIEWER	D.M.A.Wallace Associate Professor of Urology School of Surgery, Fremantle Hospital University of Western Australia
REVIEW RETURNED	07-Apr-2013

GENERAL COMMENTS	This is an important study which contributes to our understanding of why female have a worse survival for bladder cancer. The authors have been unable to differentiate microscopic from macroscopic haematuria and suggest that the majority of their
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	<p>haematurias were macroscopic. This may be very relevant for future research and application of this paper to changing practice. Could the authors discuss why they could not collect this. This might be important when it comes to further analysis of the reasons for delay in the group with no history of visible haematuria.</p> <p>No staging information is given about the bladder cancers. Cancer registries have varied in their reporting of non-invasive bladder cancers. Were all bladder tumours included or was carcinoma in situ and papillary non-invasive tumours (pTa) excluded? Was the study under powered to compare staging difference according to promptness of referral?</p> <p>The authors have calculated to total numbers of women in the UK who may be affected by delayed referral. Are they also able to calculate what the overall increase in referrals to urology departements would be if this were to be addressed? It would appear that this might be quite a modest number when compared to the total numbers being referred and could be absorbed.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Willie Hamilton, University of Exeter Medical School

1. The English is excellent. The authors desperately try to avoid the word 'delay' - preferring the word non-prompt. At times this purism is taken too far [personally, i agree that the word delay has connotations of avoidability, which may not always be apposite - but in this paper, the whold throust of the non-promptness is that it MAY BE avoidable. Thus using the pejorative word 'delay' (which would read better) is probably acceptable/appropriate.

Thank you. We have revisited the text and made changes in the spirit suggested by Professor Hamilton where it was possible to do so, mainly using the word 'timeliness' or similar.

2. The paper by Shephard (which author RN and I am co-authors on) will be published in April, so this reference can be made 'normal' in any revision.

We have now included this reference.

3. I wonder if the authors should address the clinical significance of these delays (see - I'm now using my preferred word!). It is only in the 'tail' of the distribution (the 90th centile) that women are as much as 2 months delayed. Are lesser durations important? it may also be worth mentioning the health economics of their (gentle) recommendations towards more rapid investigation of some women.

Looking at the 75th percentile values, it is apparent that a quarter of women experiences about twice as long a primary care interval than a quarter of men. We conceptualise the issue of delays in diagnosis after presentation to a GP with cancer symptoms as one that is consequential for the experience of all patients; but also one that is consequential for clinical outcomes (e.g. treatment eligibility and cancer survival) for some patients, see Discussion, 3rd paragraph, start.

“We believe that the principal reason for improving the promptness of cancer diagnosis among symptomatic patients is to ensure as positive an experience of cancer care as possible for all patients,9,10,11,12 although achieving such improvements may also help to improve treatment and prognosis for some. Indeed, there is some evidence indicating an association between diagnostic delay and worse oncological outcomes for patients with bladder cancer presenting with haematuria.31,32”

References in the above section:

31 Wallace DM, Bryan RT, Dunn JA, Begum G, Bathers S; West Midlands Urological Research Group. Delay and survival in bladder cancer. *BJU Int.* 2002;89(9):868-78.

32 Hollenbeck BK, Dunn RL, Ye Z, Hollingsworth JM, Skolarus TA, Kim SP, Montie JE, Lee CT, Wood DP Jr, Miller DC. Delays in diagnosis and bladder cancer mortality. *Cancer.* 2010;116(22):5235-42.

Regarding health economics, we have modified the end of the 4th paragraph of discussion to now read (new text is denoted in red fonts).

“.....The positive predictive value of haematuria for urological cancer is generally lower than 15% (depending on age),¹⁵ and is lower in women than men.¹⁶ This means that even in a hypothetical situation where all patients presenting to general practitioners with haematuria were referred promptly for specialist investigation, the great majority of them would be found not to have urological 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 also serve as potent reminders of the need for the development of newer tests (and particularly easily accessible and acceptable point-of-care tests) and service models.”

4. Bladder cancer is expensive business: like colorectal, the costs of diagnosis may exceed the costs of treatment (as you have to investigate so many without cancer to find the cancers. With their recommendations (which i support clinically) just how many frogs will we have to kiss to find a prince?

Please see reply to the above comment.

Reviewer 2: D.M.A.Wallace, Associate Professor of Urology, School of Surgery, Fremantle Hospital, University of Western Australia

1. This is an important study which contributes to our understanding of why female have a worse survival for bladder cancer. The authors have been unable to differentiate microscopic from macroscopic haematuria and suggest that the majority of their haematurias were macroscopic. This may be very relevant for future research and application of this paper to changing practice. Could the authors discuss why they could not collect this. This might be important when it comes to further analysis of the reasons for delay in the group with no history of visible haematuria.

Thank you for this very important comment, which has led to a substantial improvement of the paper: The analysis in 'version 1' used an aggregate definition of 'haematuria' (not otherwise denominated into macroscopic or microscopic). That operational definition did aggregate information from free text entries in a (separate) data item ('what was the main presenting symptom'), but used a semi-automated approach (in Excel) and involved no clinical input. The Reviewer's comment prompted us to re-examine the available data, and we were able to produce anew a robust definition of macroscopic haematuria (excluding microscopic haematuria presentations) going through all the available information on a record-by-record basis and using the clinical knowledge of three of the authors (GR, RDN and GL). This resulted in a small increase in the number of cases with haematuria

due to the more detailed and sensitive new coding approach. We have therefore re-run all analyses and updated the text and tables throughout, all relevant evidence now specifically relating to macroscopic haematuria. As we had originally predicted based on the literature, most 'haematuria' presentations were indeed macroscopic. The results changed little, although the paper gained greatly in sharpness of focus and in terms of relevance to future research and clinical practice.

2. No staging information is given about the bladder cancers. Cancer registries have varied in their reporting of non-invasive bladder cancers. Were all bladder tumours included or was carcinoma in situ and papillary non-invasive tumours (pTa) excluded? Was the study under powered to compare staging difference according to promptness of referral?

Unfortunately no histological type information was available. We have not presented stage data because as the Reviewer also suspected the sample size is under-powered for answering whether there is an association between gender inequalities in the timeliness of diagnosis and stage.

3. The authors have calculated to total numbers of women in the UK who may be affected by delayed referral. Are they also able to calculate what the overall increase in referrals to urology departments would be if this were to be addressed? It would appear that this might be quite a modest number when compared to the total numbers being referred and could be absorbed.

We agree with the Reviewer that addressing questions on resource use and other aspects of health economics evaluation is important. It is impossible to estimate the likely impact of improvement initiatives on referrals with the existing data, not least because in addition to information on cases such estimation would also require information on patients who present with haematuria but do not have cancer. We have suitably modified the text in the end of paragraph 4 of Discussion to address health economics analyses in general – please see also reply to Reviewer 1, comment 3, above. It should also be noted that UK guidelines by NICE (see Methods, and relevant reference) mandate the referral of patients with macroscopic haematuria, independently of their gender.

General editing / minor changes not mandated by Reviewers' comments: Please note that we have taken the opportunity to further proof read and improve the clarity of the language used and/or the presentation of the argument in a small number of instances throughout the text – where such changes occurred they are tracked. In addition, we have included a new recently published reference (34) which discusses potential factors responsible for gender inequalities in bladder cancer survival (Reference: Noon AP, Albertsen PC, Thomas F, Rosario DJ, Catto JW. Competing mortality in patients diagnosed with bladder cancer: evidence of undertreatment in the elderly and female patients. *Br J Cancer*. 2013 Apr 16;108(7):1534-40. <http://www.ncbi.nlm.nih.gov/pubmed/23481180>).

In conclusion we have been able to address all comments and substantially further improve the manuscript. We believe our paper has great potential to improve the quality of care for many women who currently experience delays in the diagnosis of bladder or renal cancer and it will be of substantial interest to general practitioners, patient groups, research funders and policy makers. We are looking forward to hearing from you.