Author’s response to reviews

Title: Cancer suspicion in general practice, urgent referral and time to diagnosis: A population-based cross-sectional study

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Author’s response to reviews: see over
Dear Editor,

RE: MS: 6417306013093734 - Cancer suspicion in general practice, urgent referral and time to diagnosis: A population-based cross-sectional study

Thank you very much for the positive assessment of our manuscript, giving us an opportunity to revise and improve it. We found the reviewers’ comments very relevant, informative and helpful. Below, you will find a detailed description of how we have responded to the individual comments and suggestions from the reviewers. For your readability we have numbered the reviewers comments and written our responses in red italics.

We have also updated reference no. 32 (now reference no. 33), as this has changed status from ‘in press’ to ‘published’.

Furthermore, as we removed the abbreviated ‘diagnostic interval’ as DI throughout the manuscript, as proposed by the reviewer, we have excluded this abbreviation from the abbreviation list.

Additionally, to enhance the readability of the manuscript, we have emphasised the actual number of cases analysed both in the abstract (line 42) and in the manuscript (line 187) and likewise emphasised which variables have been used for confounder control in the analyses (line 143).

Finally I have changed the e-mail of the corresponding author, as our institution has assigned new e-mails for all employees.

On behalf of the authors,

Yours sincerely,

Henry Jensen
REVIEWER 1 (William Hamilton)

Major compulsory revisions

1. None, other than to consider changing 'alternative' in line 268 to 'additional' – I think that’s what they mean (and it’s certainly what I mean!)

   Thank you for this point, we agree and have changed the wording accordingly.

Minor Essential revisions

2. It may not be house style, but the discussion would be easier if the section 'Comparison with other findings' had a second subhead 'clinical use of the results'. The discussion has both of these but rather hops between the two areas.

   We acknowledge this and have revisited the discussion. Therefore, we have, as proposed by the reviewer, added a third subheading in the discussion named “Clinical implications” just before the conclusion. This short subsection summarizes what can clinically be used of the results as follows:

   ‘Clinical implications

   This study underlines the importance for clinicians in general practice to consider and investigate for cancer even when the patient does not present well-known alarm symptoms of cancer. Otherwise, only a proportion of cancer patients will be provided the faster diagnostic pathway, leaving approximately half of all cancer patients to a longer period of uncertainty before diagnosis is confirmed. This implies that the GPs must have access to relevant investigations if the aim is to achieve earlier cancer diagnosis.’

REVIEWER 2 (Suzanne Scott)

Minor Essential Revisions

The major limitation to this research is that a key variable ‘GP’s interpretation of symptoms’ is obtained at the point of the research study rather than at the time the GP made the assessment of the patient. This opens the data to bias. For instance, given that the GP now knows that patient has now gone on to be diagnosed with cancer, they may, in hindsight look at the recorded presenting symptoms and indicate that they are ‘alarm’ symptoms suggestive of cancer. Although this appears to be hinted at in the discussion (lines 223-225), this needs to be emphasised in the discussion as a main limitation.

   We absolutely agree this is a very important point. We acknowledge that it can be of major concern in a study like this. Therefore, we have emphasized this in accordance with the reviewer’s comment, and changed the wording as follows:

   ‘Even so, the retrospective nature of the questionnaire may imply the risk that some of the GPs may have misinterpreted the symptoms of a particular case and hence may have overestimated the proportion of cases with guideline-based ‘alarm’ symptoms. This would tend to underestimate the association between the GPs’ assessment of ‘alarm-symptoms’, use of CPP and the diagnostic interval’

The manuscript varies in referring to the GP’s interpretation of symptoms (the correct expression) and that the patient HAD alarm symptoms/vague symptoms etc (the latter in incorrect given that this variable is the GP’s subjective evaluation (as noted by the authors), what constitutes alarm symptoms will differ). Consistence is needed throughout and should always include reference to GP’s interpretation (e.g. ‘Patients who had symptoms interpreted to be alarm symptoms’ rather than ‘patients who had alarm symptoms’).
Thank you so much for pointing this out. To avoid any misunderstanding for the readers, we have, as proposed by the reviewer, included reference to the GP’s interpretation throughout the manuscript.

Given that GP’s interpretation appeared to be strongly associated with time to diagnosis (acknowledging the limitation of this variable, as specified above) then more attention should be given to this. The authors note that the first symptoms were recorded (line 115) but do not present any data – are there any symptoms that were consistently misinterpreted by GP’s as not suggestive of cancer? This would be useful information for future interventions.

The aim of the study was to examine the GP’s interpretation of the first presentation and the use of CPP and the diagnostic interval. Therefore, it would not be valid to ask only for predefined, guideline-based symptoms that might or might not be indicative for cancer in clinical general practice. It is, as noted by the reviewer, much more interesting that the clinical assessment of the patient made by the GP has such important influence on what is going to happen with the patient. If we also included analyses of the symptoms registered by the GPs (which may not be complete or valid) we would 1) go beyond what can be presented in one paper and 2) introduce aspects that would imply that e.g. guidelines in cancer suspicion are evidence-based, which is not always the case. Therefore, we have deleted the information of symptoms in the text and only focusing on the GP’s interpretation by rephrasing the sentence as follows:

‘The questionnaire focused on information about the GP’s interpretation of the symptoms presented by the patient at the first consultation by asking the GP: ‘How did you interpret the symptoms?’ The GP was given three possible categories to answer: alarm symptoms suggestive of cancer (alarm), symptoms suggestive of any serious disease (serious), or vague symptoms not directly suggestive of cancer or other serious disease (vague).’

Abstract
3. Line 50. Use ‘duration’ rather than ‘length’
   We agree and have changed the wording as proposed.

Introduction:
4. The introduction is very brief and would benefit from expansion in places to add more background / clarity to the issues raised. For instance:
   We agree, and have added additional information as proposed below

5. Line 61- explain the 2WW system and how ‘low’ was uptake?
   Thank you for pointing this out, we have rephrased the sentence with more information on the 2WW and also examples of the low uptake based upon the same references:

   ‘The UK have introduced two-week wait referrals (2WW): referrals where the GP suspects cancer and refers the patient as urgent, meaning the patient should be seen by a specialist within two weeks. To qualify to be referred as urgent to a 2WW, the patient need to fulfil the criteria outlined in the NICE guidelines. Previous studies of the British 2WW referrals have shown that the general practitioners’ (GPs) use of 2WW referrals was from one in five to one in three of cancer patients and that patient not referred urgently had significantly longer duration of the time to diagnosis [8-13].’

6. Line 61/62 – in what way is length (duration) of time to diagnosis effected?
   Very good point. We have rephrased the sentence adding information how the use and no use of 2WW affects the duration of time to diagnosis.

7. The setting (currently outlined in the methods – lines 87-97) would be better placed in the introduction
Thank you for this idea. We have checked and do agree that some of the setting (the explanation of the Danish CPPs) would be better placed in the introduction. Still, we have placed some of the setting (incidence rate of cancer and the organization of the primary care) in the Methods section, as to keep a natural flow in the introduction. Hence we have moved the description of CPPs to the introduction lines 66-72 incorporating it just after the description of the UK two-week wait:

‘In 2007-2009, CPPs were introduced in Denmark for diagnosis and treatment of suspected cancer as part of the Danish National Cancer Plan II [2,14]. The Danish CPPs consisted of guidelines, descriptions of selected alarm symptoms that may raise cancer suspicion and well-defined diagnosing schedules from clinical suspicion of cancer until treatment, including specific time frames, hence the Danish CPPs can be seen as comparable to the 2WW in the UK. The five Danish regions (i.e. the hospital owners) were given three months to implement the guidelines at local level [2]. By spring 2009, CPPs for 32 specific cancers had been developed [2,3].’

8. Did the researchers have any hypotheses? What were these and why?

Our hypothesis was that there would be a difference between the groups depending on the GPs’ assessment of severity/degree of suspicion and that would influence the use of CPP and diagnostic interval in the way we found. We realise that we have not been explicit about that and have now introduced this just prior to the description of the aim:

‘For these reasons we hypothesized, that when the GPs’ suspected cancer based upon the patient’s symptoms the GP would be more likely to use CPP than when the GP did not suspect cancer. Furthermore we suspected that this would influence the duration of the diagnostic interval by longer diagnostic intervals for those patients, where the GP did not suspect cancer and also for those patients not referred to a CPP.’

Methods:

9. Line 102/103 – For those with no GP involvement, how did they enter the system?

We have added a sentence, following the sentence in question, explaining how the remaining entered the system. The sentence is as follows:

‘The remaining patients were diagnosed through screening (6.1%), emergency access or as coincidental findings during diagnostics of other illnesses.’

10. Line 115 – Information on symptoms. What was used to gather this information.

As mentioned above we have now explained that we do not use information on symptoms in this study and therefore we have omitted this description of the method. To avoid misunderstanding we have rephrased the sentence to clarify that only the information on the GPs symptom interpretation was used.

11. Given that the study covers all cancers, what symptom list what used and why?

Very good point. We used a list consisting of the 20 most common reported symptoms among Danish cancer patients in general practice (ref: Nielsen TN, Hansen RP, Vedsted P: [Symptom presentation in cancer patients in general practice]. Ugeskr Laeger 2010, 172:2827-2831.) with an option to provide additional symptoms in free text. This method has previously been used and tested in Danish settings. Yet, as mentioned above, we have now omitted this information in the text as we do not use the data in this paper.

12. Line 116 – please provide the exact question used regarding GP interpretation
Very good point. We have added the question to the sentence:
‘The questionnaire focused on information about the GP’s interpretation of the symptoms presented by
the patient at the first consultation by asking the GP: ‘How did you interpret the symptoms?’ with
three possible categories for the answer: alarm symptoms suggestive of cancer (alarm), symptoms
suggestive of any serious disease (serious), or vague symptoms not directly suggestive of cancer or
other serious disease (vague).’

13. Line 124 – write out in full rather than using abbreviations
   Good idea, we have done so with the abbreviations in brackets.

14. Line 140 – Statistics Denmark requires a reference
   Good point and we have added the reference ‘Thygesen LC, Daasnes C, Thaulow I, Bronnum-Hansen H:
   Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation,

Results:

15. Line 176 – what is meant by ‘distant’ tumour? – provide definition; ‘stag’ should be ‘stage’
   Thank you for pointing this out to us. We have rephrased it into ‘...distant tumour stage (metastatic
cancer)’.  

16. Given the data presented in Table 3, Table2 seems of limited value and could be removed.
   We partly agree, as Table 2 offers the distribution of the use of Cancer Patient Pathways (CPPs) across
   the cancer sites and shown for gender, age and GP’s symptom interpretation, whereas Table 3 is the
   adjusted chance to be referred to a CPP. We acknowledge that these tables are complementary, but we
do think that some readers would prefer the exact numbers referred to a CPP (Table 2).
   We have tried to combine table 2 and 3 into one, but this resulted in a very wide table consisting of 29
   columns with a much reduced readability. Therefore, we suggest keeping both tables to accommodate
   all readers’ preferences.

17. Line 187/186 – include statistics when referring to significant differences
   We have added the prevalence ratio to this sentence

18. Lines 187-190 – There is no mention of the findings regarding age here yet the Table indicates there might
   be some differences. If this is the case it might be worth describing them in the text.
   Thank you for directing our attention to this. Initially, we disregarded this in the text, as these findings
are not general trends seen in the data, and we tried to focus on the general trends in the text. But, we
do acknowledge the point made, and have described the findings by adding the following sentences at
the end of the paragraph:
   ‘Furthermore, even though no overall association between age and CPP referral was observed, breast
   cancer patients aged 45-64 were less likely to be referred to a CPP (Table 3).’

   Thank you for pointing this out to us. We totally agree and have changed the wording as proposed.

20. In all Tables ‘symptom interpretation’ should be ‘GP’s symptom interpretation’
   Very good point. We have changed the wording in all tables as proposed to be consistent
21. The text (Lines 187-190) indicated that there were no significant associations with referral to a CPP (apart from GP’s symptom interpretation) once adjustments were made yet in Table 3 (in which the title notes adjustments have been made) there are significant associations (highlighted in bold) for gender and age. 

   *Sorry for this confusing. What we meant was that the significant associations only remained for referral to a CPP after adjustment across all cancer sites. We have emphasized this, by rephrasing the sentence as follows:*

   ‘Only the GP’s symptom interpretation remained statistically significant associated with CPP referral, across cancer sites, after adjustments, except for malignant melanoma for which no association was found (Table 3).’

22. Tables 5 – ‘Referral mode’ rather than ‘Referral scheme’ to be consistent with other tables

   *Thank you to point this out to us. We have changed the wording as proposed*

23. It would aid clarity if the order of the variables in the tables was the same throughout

   *We agree, and have changed the order in the tables to be same throughout*

**Discussion:**

24. Lines 244-246: expand on what is meant here

   *This is a very good point. What we mean is that the criteria behind ‘reasonable suspicion of cancer’ is based upon so called red flags symptoms very much like the NICE guidelines. But approximately 50% of cancer patients do not present with these red flag symptoms.*

   *We have elaborated on this in the manuscript in lines 259-262:*

   ‘The reasons for these results remain unknown, but it may be suspected that the criteria behind the ‘reasonable suspicion of cancer’, is too specific to target the patients‘ symptomatology in general practice, as up to 60% of cancer patients do not present with alarm symptoms [19,20]. This issue has also been raised as a concern in the UK [8-13].’

**Discretionary Revisions**

25. Suggest diagnostic interval is not shortened to DI

   *We appreciate this proposal to increase the readability of the manuscript. We have amended as proposed.*