Author's response to reviews

Title: Socioeconomic Patient Characteristics Predict Delay in Cancer Diagnosis: a Danish Cohort Study

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

Thank you much for the constructive feedback. We hereby submit a revised edition of our manuscript 'Socioeconomic patient characteristics predict delay in cancer diagnosis: a Danish cohort study', addressing the comments from the referees. Some general comments to the reviews and a point-by-point response to the referees’ concerns follow below.

General comments:
Tables: The referees have different views of the number of tables necessary and the contents of the tables accompanying the article (Referee 2, 10; Referee 3, 2 and 4). We have carefully considered this issue and have chosen to keep the four tables as they add valuable information to the study. As requested by Referee 2 (Referee 2, 3) a new table has been added that shows the distribution of cancers in the study (see revised manuscript, Table 1).

General approach versus diagnosis-specific cancer approach: The referees have different opinions regarding the pooling of cancer diagnoses in the study (Referee 1, 4; Referee 2, 3). We pooled all the different cancer diagnoses when analysing the data as one of the main ideas of this study was the adoption of a general practice approach to symptoms, viz. that the patient attends the GP with a symptom that may be related to cancer in general and not to a specific cancer diagnosis, and that the patient seeks help to interpret this symptom. The fear of serious disease such as cancer, but not of a specific cancer type, is the key element in the patient’s help-seeking behaviour\(^1\), and this behaviour is not solely guided by his or her awareness of a possible specific cancer type, but more by personal symptom interpretation. Research into patient delay among breast cancer patients suggests that the patient’s initial symptom interpretation, i.e. the stage where the patient determines whether medical attention is required or not, accounts for most of the delay variation\(^2\). In addition, GPs also act on symptoms although their interpretations also include a judgment about the “alarmingness” of the symptoms. Finally, the logistics and the capacity in the part of the secondary health care system that primarily performs the diagnostic examinations are not considered to be diagnosis-specific. On these assumptions, we therefore designed and analysed the study with all cancer diagnoses pooled. The basis of this approach is explained in the discussion (see revised manuscript). Future studies from our department will cover the examination of cancers by type.

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Referee 1:

**Major compulsory revisions:** We have changed the way the results are presented according to the reviewer’s suggestions. Subheadings are provided for all categories (see revised manuscript).

**Minor essential revisions:**
1. SE status treated as a binary variable: Initially, we analysed the predictors “Household income” and “Household fortune” in three categories: “low, middle, and high” and “small, medium and large”. The two first mentioned categories within each predictor category were later combined as no major differences were found in the estimates (data available on request), and the proposed U-shaped relationship was not found. The categories correspond to a low/middle income of <65,000 €; a high income of ≥65000 €, a small/medium fortune of <130,000 €, and a large fortune of ≥130,000 €. These amount limits are applicable to Danish conditions.

2. References to a submitted paper [Hansen et al]: We are waiting for the review comments and hopefully acceptance of this submitted paper. Main results of this paper are outlined in the present paper to explain the quartiles (delay results). There is only one reference to the submitted paper in the revised manuscript.

3. Justification of an approach merging all cancers: We agree on this important consideration, and are aware of the work by Macleod et al. See general comments.

4. Approval of a symptom-based approach. See general comments.

5. Discussion of results compared with a former study by Neal & Allgar. A further discussion is provided regarding differences in study population, culture and health care system organisation (see revised manuscript).

6. Quality of written English: A competent Professor and MA in English for medical science has revised the manuscript.

Referee 2:

1. Importance: Interventions aimed at targeting improvements reducing delay (e.g. focus on risk factors, campaigns targeted at specific age groups, social classes etc.) are described in the background section (see revised manuscript).

2. Background: The statement about “delay and prognosis” is refined in the background section and the literature on socioeconomic characteristics and different delay types has been extended (see revised manuscript).

3. Methods. Analysis of all cancers together: We acknowledge the referee’s point of view, but we maintain the general approach as we find it important to investigate if general characteristics can be found across cancer diagnoses. See general comments. A table of the numbers of each cancer in the data set has been added (see revised manuscript – Table 1).

4. Statistics: The initial manuscript lacked a model of how much significant factors contributed to the estimates presented and how much of the variance this explained. We have added such a description in the revised manuscript (see result section). In addition, the words “unadjusted analyses” have been
replaced by “univariate analyses” and “adjusted analyses” by “multivariate analyses” for clarification.

5. Missing data: Analyses of non-responders (patients as well as GPs) revealed no major discrepancies between participating and non-participating patients/GPs with respect to age, gender or distribution of cancer diagnoses (see revised paper) (data available on request). The completeness of the HDR of e.g. haematological malignancies and ovarian cancers was found to be 91.5 and 96%, respectively, compared with data from the Danish Cancer Registry\textsuperscript{3,4}.

We excluded cancer cases outside the time period (inclusion period) as one of the subsidiary aims of the study was to conduct a descriptive study of delay in the county in a 1-year period. We are in agreement with the referee’s comments, but we accept to reject otherwise applicable data, as we find the present study population large enough to perform the described analyses.


6. Definition of delay: We agree that the mentioned reference for “widely used” needs to be updated, but we decided to remove this sentence in the revised manuscript.

The authors agree on the difficulty of defining “the date of first symptom”. It can be complicated for GPs (and patients) to accurately define and recall each type of delay. We encouraged the GPs to estimate the number of weeks the patients had postponed attending their GPs with the first symptom of a cancer. GPs in Denmark are required to keep medical records, and most GPs will have information on these issues in their records. We also obtained delay information from patients, and we learned from the questionnaires that both patients and GPs tended to state the date when the cancer suspicion was definitively raised as the date of the patient’s first perception of cancer symptoms, and thereby both patients and GPs probably tended to underestimate patient delay. We compared the GP-reported with the patient-reported delay, and no major discrepancies were found in any of the delay phases (see table below) (see revised manuscript). In conclusion, the questionnaire approach probably underestimated patients’ and GPs’ specification of patient delay, but we do not suspect any systematic misclassification between the “true values” and the specifications of doctor- and system-related delay as patients and GPs had more date indicators to rely on (e.g. first in-hospital visit and initiation of treatment). This may imply that we cannot detect associations related to patient delay, but we have no reason to believe that we underestimated associations in relation to doctor or system delay.

<table>
<thead>
<tr>
<th></th>
<th>Total delay</th>
<th>Patient delay</th>
<th>Doctor delay</th>
<th>System delay</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Median IQI</td>
<td>N Median IQI</td>
<td>N Median IQI</td>
<td>N Median IQI</td>
</tr>
<tr>
<td>GP-reported delay</td>
<td>936 98 57-168</td>
<td>1237 21 7-56</td>
<td>1877 0 0-2</td>
<td>1422 55 32-93</td>
</tr>
<tr>
<td>Patient-reported delay</td>
<td>747 108 61-194</td>
<td>900 16 2-61</td>
<td>851 0 0-7</td>
<td>847 55 32-96</td>
</tr>
</tbody>
</table>

*IQI=interquartile interval

In order to enable subdivision of delay, the analyses were restricted to pathways where a GP was involved in the diagnosis. Emergency or out-of-hours cases and other activities outside normal GP working hours were excluded, as we were only able to calculate system delay in secondary health care in these cases (see revised manuscript).
Data were analysed using a logistic regression model to estimate the likelihood of long delays. This model was chosen to be able to show the contrast between long with short delays. The delay data were far from being normally distributed which hampers the use of continuous data. In addition, we could have used ordered logistic regression and proportional hazard models, but these methods did not comply with our aim of contrasting long and short delays. Median doctor delay was 0 days and the 75th centile was 2 days. The low 75th centile value for doctor delay was confirmed in the patient-reported delay data (see table above).

7. Our choice of predictors was primarily guided by relevance as ascertained through critical literature studies where socioeconomic status is conventionally studied along the three dimensions education, occupation and income. Educational level remains relatively stable beyond early adulthood and is thus less affected by changes in health status than income and occupational status. The selected questions were slightly modified from a widely used model questionnaire from the Danish Institute of Public Health. Patient comorbidity was assessed in the GP questionnaire but this falls outside the scope of this paper. It will be dealt with in a future paper.

8. The patients were identified as potential study participants as soon as they were identified in the HDR, which means that on average the patients were identified and sent a questionnaire one month after the diagnosis (see revised manuscript).

9. Results: See general comments. We cannot exclude that some of our statistically significant findings are caused by multi-significance (see revised manuscript – discussion). Future studies should address this issue.

10. Discussion and conclusion: A more critical discussion of the difficulties and limitations of the study is provided (see revised manuscript). The point that comorbidity may be confounding alcohol and tobacco use is interesting and will be addressed in future studies.

11. The use of the word “delay”: We agree with the referee that the use of the word in the literature – and thus in this article – is misleading and unduly negative. We would like to take an active share in the development of a better term; but so far we refer to its operationalisation in the literature, so as not to confuse the readers.

Referee 3:
Major compulsory revisions:
1. Background: The background section has been extended according to the comments of the reviewer here and of reviewer 2, 2 (see revised manuscript).

2. Reporting of unadjusted analyses: We chose to report both uni- and multivariate analyses to enable the reader to monitor the data throughout the processing.

3. Interactions: We did not find statistically significant interactions between smoking/drinking and socioeconomic status (see revised manuscript - results). We conducted Hosmer-Lemeshow goodness-of-fit tests on our multivariate models and found that the models fitted to a satisfactory extent.

4. Table 4: See general comments.
5. Screening: Until now there has been a conservative approach to screening in Denmark. A national systematic breast screening programme is scheduled to begin in January 2008, and systematic PSA screening is not done in Denmark. We therefore maintain that most breast cancers are palpable at the time of first GP consultation in this patient cohort and that patient delay is a relevant parameter for all cancer types, but we agree that the referee’s comments are highly relevant to other patient cohorts.

6. Implications of the study: In the implication section we suggest that the fact that male patients downplay the importance of their symptoms may explain that male patients experience longer doctor delays than female patients. We believe that gender-specific cultural differences exist and encourage future research within this field.

9. Implications of the study: The authors have no evidence that large household fortune and education are proxies for a better ability to describe symptoms. This is meant as a suggestion, not as evidence.

10. The universal access to health care in Denmark might theoretically imply that all patients in the cohort had the same delays. The findings of some differences may indicate that personal differences and differences in symptoms play a role, but, in general, only few socioeconomic predictors of delay were found, and as there are only small socioeconomic inequalities in Denmark, we conclude that our findings concerning socioeconomic characteristics and delay in cancer care do not have major implications for health care provision in this setting (see revised manuscript).

Minor essential revisions:
1. The description of the “delay” variables has been moved to the “outcome measures” section (see revised manuscript).

All authors included on the paper fulfil the criteria of authorship. Any necessary research ethics committee approval was obtained for the study. All authors declare no competing interests.

Yours sincerely,

Rikke Pilegaard Hansen (on behalf of all authors)