Author’s response to reviews

Title: Factors related with symptom duration till diagnosis and treatment of symptomatic colorectal cancer

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

We are pleased to send you the manuscript. ‘Factors related with symptom duration until diagnosis and treatment of symptomatic colorectal cancer’ for new consideration after inclusion of editor suggestions. English language has been reviewed all over the manuscript and specially new sentences added during revisions. We expect it will be satisfy you.

Particularly, the sentence ‘While there is recent rigorous literature on time duration to cancer diagnosis or treatment, most of it is old and presents methodological issues that need to be taken into account, such as different ways of measuring symptom duration and accuracy in recording symptom presentation [4-5]. ”, has been slightly changed. Papers 4-5 reflect the methodological issues encountered in the studies on delay influence on survival or stage. Much of the studies reviewed were old.

Yours sincerely,

Magdalena Esteva

Corresponding author
Answers to Una Macleod

In the second paragraph of Background we changed Walker et al for Walter et al.

Answers to Reviewer: Rosemary Tate

Reviewer's report:
The paper has been very much improved w.r.t. the univariate analyses. However, there has been little change in reporting of the multivariate survival analysis, which was my main concern.
I suggest that the section on survival analysis is removed since the model seems inappropriate and may lead to incorrect conclusions. Also, it does not add very much to the final conclusions. I wonder if it was added as an afterthought since this was originally described as a descriptive study?
If the authors choose to follow my advice and remove the section on survival analysis, then most revisions are very minor. Otherwise major revision is required.

After discussion with all manuscript's authors, we have agreed to follow your suggestions in terms of removing survival analysis. As you mentioned, it does not add very much to the final conclusions and is difficult to interpret. For this reason we have changed:
Abstract : Background fist sentence removed in order to shorten the abstract. Also we removed survival analysis and EXPANDED bivariate results.
Methodology: we have removed survival analysis in pg 9 and references 20, 21 and 22.
Results: removed last paragraph and table 6
All references from reference 20, have been reordered.

We think that our cross sectional study could, in some way, be considered a retrospective cohort. In the future, we will continue to work in assessing the behavior of those variables related with investigations which occur during the diagnosis time interval which are involved in possible important breakdowns in the diagnosis process.
In our analysis, assumptions of proportionality were tested in those variables with p<10 in the bivariate analysis. Results showed not proportionality in those variables concerning investigations or explorations. When we tried to find out an explanation for non proportionality, and consulting literature, we really noticed that they appeared in some time during the diagnosis or treatment process and could be considered time dependent. We think this fact merits further evaluation in future analysis.

This has been quite difficult and time-consuming to re-review as most of the
responses do not show where (or if) changes were made in the text. I have therefore had to hunt around for them. I also found some new changes that were not in the original document, and were not mentioned in the response. In future I would ask the authors to indicate where all changes are made with page and paragraph numbers as is usual for a response.

We are very sorry about that, this time we tried to better organize our responses,

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Detailed comments – I have annotated the relevant sections of my original review and the response with my new comments in capitals
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Major revisions:
4. For the Cox model, were the assumptions of proportionality tested and if so what was the result? This needs to be reported. (Alternatively a Poisson model may be more appropriate)

We have changed a little bit the explanation of survival analysis. Including results of proportional test would be long and we thing would not give essential information.
YOU NEED TO SAY WHETHER OR NOT THE PH ASSUMPTIONS WERE MET AS IF THEY WEREN’T THIS MODEL IS NOT VALID.

A multivariate Cox proportional hazard model with time-dependent covariates were performed to allow covariates change their values over time. For example a patients has a value of hemogram zero until the time the hemogram is done, and 1 after that moment.

IF THE MULTIVARIABLE MODEL IS TO BE INCLUDED, A MUCH MORE THOROUGH REPORTING OF IT IS REQUIRED, BOTH IN THE METHODS AND THE RESULTS. THERE IS VERY LITTLE MENTION OF THESE RESULTS IN THE CONCLUSIONS, SO FOR SIMPLICITY, I SUGGEST IT IS BETTER TO DROP THIS PART ALTOGETHER.
I REMAIN UNCONVINCED OF THE APPROPRIATENESS OF A TIME-DEPENDENT COX MODEL, SINCE MOST OF THE “TIME-DEPENDENT” VARIABLES ARE PART OF THE DIAGNOSIS PROCEDURE. HOWEVER, IF THEY ARE INCLUDED AS TIME-DEPENDENT, THE METHODS TO DO SO AND RESULTS OF HOW THIS TIME RELATES TO THE OUTCOMES NEEDS TO BE EXPLAINED IN MUCH GREATER DETAIL.
THANK-YOU FOR POINTING ME TO THIS (EXCELLENT) ARTICLE BY FISHER AND LIN. CONTRARY TO SUGGESTING THAT THIS METHOD IS APPROPRIATE, THEY WARN AGAINST IT AND, INDEED, EXPRESS MY
CONCERNS VERY ELOQUENTLY. PARTICULARLY IN THIS SENTENCE IN THE SECTION ON INTERPRETATION  
“IN GENERAL IF TIME-DEPENDENT COVARIATES CAN CHANGE IN RELATION TO HEALTH OR SOME OTHER GENERAL CONCEPT RELATED TO THE ENDPOINT IN THE MODEL, THEN INTERPRETATION IS DIFFICULT AND PRONE TO BE MISLEADING. GREAT CAUTION IS ADVISABLE.”

7. The result that family history of cancer is positively associated with delay seems surprising and counter-intuitive. This result needs checking and further investigation. I note that 45% of patients reported this family history of cancer, which seems rather high – although again this variable is not described, so I can only assume it must relate to non-immediate family and all types of cancer (including very common benign skin cancers?)

There were all type of cancers (not benign skin cancer) we concretely asked for parents, children, spouse, brothers or sisters, any other family member and friends. There are few studies on delay and family history of cancer but when looking to breast cancer screening, some studies show women more reluctant to participate in screening if there is previous familiar or quittances with cancer because fear of some cancer findings is higher.

IN THIS CASE IT IS NOT FAMILY HISTORY THAT YOU ARE LOOKING AT, BUT EXPOSURE TO SOMEONE CLOSE WHO HAS CANCER. PLEASE MAKE THIS CLEAR AS THIS IS SOMETHING QUITE DIFFERENT. ALSO, HAVE YOU CONSIDERED THAT THIS VARIABLE WILL BE RELATED TO AGE, SINCE THE LIKELIHOOD OF THIS HAPPENING WILL INCREASE WITH AGE, AND IN FACT MOST OLDER PEOPLE WILL BE BOUND TO HAVE HAD THIS EXPERIENCE?

In table 2 He have changed family history of cancer by history of cancer in family and quittances. We agree with you that aged patients have higher experience in history of cancer in family members or quittances. But in our study age is not be related with longer intervals, then probably there is no confusion. We included a paragraph in the discussion, pg 12 last paragraph, last 6 lines and also added references 1 1, 10 and new ones 36 and 37. 

8. The results of the Cox regression are very unclear and I’m not really sure why these are included as so little is said about the results. This is the first time symptom duration has been mentioned – presumably you mean symptom diagnosis interval?

We have included some changes in the results of Cox regression to better clarify and eliminated symptom duration. After multivariate analysis, factors independently associated with a longer SDI and STI in CRC patients were: female gender, not visiting the doctor when he/she felt the first symptoms, the number of GP visits for CRC symptoms before referral, the absence of CRC suspicion in the GP referral letter and not performing the investigations prescribed by hospital doctors. Abdominal occlusion is related to a shorter treatment time interval but not with diagnosis interval (Table 6)"
“While there is substantial literature on time duration to cancer diagnosis or treatment, most of it is very old”

THIS IS NOT TRUE, THERE IS SUBSTANTIAL RECENT LITERATURE ON THIS – I MYSELF HAVE WRITTEN TWO RECENT PAPERS, ALSO NEAL ET AL AND MANY OTHERS THAT ARE CITED IN THIS PAPER. PLEASE CHANGE.

This statement was not our 1st version. But as a suggestion of Una Macleod (reviewer), we introduced the sentence you mentioned above (I do not know if editor have sent you all reviewers suggestions and responses to them). We know that recent literature is very important as it is cited in this paper and much more rigorous. As there are controversial suggestions between reviewer’s, we have changed the statement to a less imperative one. See pg 6 second paragraph

While there is recent rigorous literature on time duration to cancer diagnosis or treatment, most of it is old and presents methodological issues that need to be taken into account, such as different ways of measuring symptom duration and accuracy in recording symptom presentation [4-5].

Minor revisions

p<0.02 should be changed to actual p-value unless p<0.001

Done, in table 3 would you recommend your GP?, p=0.02

1rst should be changed to first or 1st throughout

Changed all over the tables

In the tables the unit of time should be stated (days)

DONE

References 13. The title of ref 53 is incorrect. It should be: Determining the date of diagnosis – is it a simple matter? The impact of different approaches to dating diagnosis on estimates of delayed care for ovarian cancer in UK primary care.

Changed

I SEE YOU HAVE REMOVED THE ABOVE REFERENCE – DID YOU MEAN
Finally we have included both references (49-50) as Tate et al paper is interesting because it discusses information issues in diagnosis data and date and first symptom presentation date.

To the sentence: Furthermore, some of the symptoms described to doctors may go unrecorded .... We added ‘as highlighted by some authors’