Author’s response to reviews

Title: Colon cancer patients with a serious psychiatric disorder present with a more advanced cancer stage and receive less adjuvant chemotherapy - A Nationwide Danish Cohort Study

Running title: Are psychiatric patients with colon cancer oncologically undertreated?

Authors:
Linda Kaerlev (Roersoe@gmail.com; l.kaerlev@dadlnet.dk; d268380@dadlnet.dk; linda.kaerlev@rsyd.dk)
Maria Iachina (Maria.Iachina@rsyd.dk)
Oleg Trosko (Oleg.trosko@rsyd.dk)
Niels Qvist (Niels.Qvist@rsyd.dk)
Pernille Møller Ljungdalh (Pernille.Ljungdalh@rsyd.dk)
Bente Mertz Nørgaard (Bente.Noergaard@rsyd.dk)

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Author’s response to reviews:

This letter to the editor and reviewers is also attached as a supplementary file in the submission section to keep the Table included correct.

Colon cancer patients with a serious psychiatric disorder present with a more advanced cancer stage and receive less adjuvant chemotherapy - A Nationwide Danish Cohort Study

Running title: Are psychiatric patients with colon cancer oncologically undertreated?.

Comments for the editor and the reviewers.

7 September 2018

Dear Editor Roberto Passera, PharmD PhD

BMC Cancer https://bmccancer.biomedcentral.com/

and reviewers.
Thank you for reviewing our manuscript. We are grateful for the useful comments with suggestions which have improved the article. Please find our listed point to point responses to these comments below. We hope that you find our article suitable for publication.

Text marked in red is included in the article. Text marked with blue is deleted in the article.

Yours sincerely

Linda Kaerlev

Reviewers’ comments:

Reviewer 1:

Subhojit Dey, MBBS, MD(AM), MPH, PhD (Reviewer 1): This is a good study with large sample size and robust methods. I just have one suggestion for the authors:

1. The possible reasons for the findings presented in this manuscript have not been elaborated adequately in the discussion section. Only the last paragraph of the "Strengths and limitations" section provides some possible explanation. I think that this explanation must be given a more central position in the discussion and must be elaborated further. This might be one of the first and unique studies on this topic but further insights about the reasons behind the findings of this manuscript will be very important in determining the future direction of similar research. This is not necessary but highly recommended.

Reply: Thank you for your suggestion. We are grateful for the useful comment. We agree and we have now included a sentence in the discussion section, p 14, line 5-9 from above: “The reasons and the clinical consequences needed to be investigated further. Possible explanations for further studies include delays in symptom recognition or in the initial presentation of the CC, difficulties in communication, diagnostic delays or other factors in the primary or secondary healthcare system.”
Reviewer 2:

Stefano Rosso, M.D. M.Sc. (Reviewer 2): The study's results showed a weak association of previous psychiatric disorders and a possible delay in the diagnosis or in treatment of CC patients.

a) However, the selection of the cohort in the study may have led to a selective removal of psychiatric patients at the very beginning. Indeed, removing patients not alive 30 days after surgery may have removed proportionally more psychiatric patients with more severe initial conditions, including a delayed diagnosis. A quick-&-dirt chi-square test on the 44 over 466 psychiatric patients versus 1659 over 29897 reference patients showed a statistically significant unbalance.

Reply:

We are grateful for the useful comment. We decided before the study started to exclude the short term survivors after their operation, but keeping them in the analyses did not change the results of the study.

We agree that we have not described this issue clearly enough. We have corrected the paragraph in the method section, p.6, line 9-13:

“A priori in the study design phase we decided to make restrictions to the study population. Observations were excluded if the patients were not operated for the cancer with a registered date of the operation. To avoid that perioperative complications had influence on the choice of treatments, and to ensure that the patients were alive long enough to be offered an oncological treatment, observations were excluded if the patients died within the first 30 days after their operation”. Deleted:”observations were excluded if the patients died during the postoperative period (30 days) (n=1,703; 44 in the psychiatric diagnosis group, 1,659 referents) (Figure 1)”

In the result section page 10 in the first paragraph line 1-7 we have corrected the text

Figure 1 shows the selection of all the CRC (cohort 1), CC and RC only (cohort 2 and 3)) used for the present study, and the subgroups of elective and the acutely operated CRC used for the supplementary descriptive statistic in Table 1. A total of 1,703 CRC patients (44 in the
psychiatric diagnosis group, 1,659 in the reference group) died within the first 30 days after operation and were excluded, leaving a total of 25,194 CRC patients (422 with a pre-existing psychiatric history, and 24,772 in the reference group) alive at least 30 days after their operation for the study (Figure 1).

Furthermore we have included a box in Figure 1 page 19, (showing the number of removed cases not alive 30 days after their operation):

Furthermore, we have included a paragraph in the discussion section, p. 14 last paragraph:

“There may have been a difference in the initial CRC stage and comorbid disease stages in patients with a pre-existing psychiatric disorder compared with patients without a pre-existing psychiatric condition, and especially among those patients who died within the first 30 days. By only selecting patients, alive at least 30 days after surgery for the study population may have removed proportionally more patients with a pre-existing psychiatric disorder with a more advanced disease. The finding of a more advanced disease in the psychiatric group might thus be underestimated, although we have adjusted the analyses for cancer stage as a possible confounding factor”.

B1) Authors did not provide details and justification about the model (type, fit, diagnostics) used for controlling confounding effects and how it was built. From text and table it can be inferred that controlling variables were all included without further scrutiny. Given the characteristics of used variables (socioeconomic status and education, or cancer stage and co-morbidity) a certain degree of collinearity could be present (and partly explaining results).

Reply: We have made the analyses as a stepwise approach and we have included the relevant confounders stepwise as already written in the article. “We adjust for each of the possible important confounders: gender, age and the Charlson comorbidity index score, pathological cancer stage (UICC cancer stage I-II versus III -IV) [24], socio-economic position (four levels), and educational level (three levels) in the adjusted analysis model. After each adjustment step we evaluated the corresponding OR with 95% CI.
The result of the unadjusted analyses as well as adjustment for 3 factors (model A) and all 6 factors (model B) is provided below:

Odds ratio for receiving intended curative treatment, and for oncological treatment by cancer site and psychiatric history, adjusted for three and for all six possible confounders

<table>
<thead>
<tr>
<th>Procedure, number (%)</th>
<th>Model A</th>
<th>Model B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude OR</td>
<td>95% CI</td>
<td>Adj. OR</td>
</tr>
<tr>
<td>Intended curative therapy, f, g, all CC+RC (N=422) (N=24,772)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (reference)</td>
<td>308</td>
<td>19,392</td>
</tr>
<tr>
<td>Yes</td>
<td>38</td>
<td>2,272</td>
</tr>
</tbody>
</table>

Oncological treatment h, CC patients only (N=301) (N=16,340)

<table>
<thead>
<tr>
<th>Procedure, number (%)</th>
<th>Model A</th>
<th>Model B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude OR</td>
<td>95% CI</td>
<td>Adj. OR</td>
</tr>
<tr>
<td>No (reference)</td>
<td>193</td>
<td>9,519</td>
</tr>
<tr>
<td>Yes</td>
<td>108</td>
<td>6,821</td>
</tr>
</tbody>
</table>

Oncological treatment h, RC patients only (N=121) (N=8,432)
No (reference) 64  52.89  4,011  47.57  1.0  1.0  Reference  1.0
Reference

Yes  57  47.11  4,421  52.43  0.81  (0.56-1.16)  0.73  (0.50-1.07)  0.72  (0.46-1.11)

a Psychiatric disorder cases = having had a history of hospital admission for at least one psychiatric diagnosis as the primary diagnosis according to ICD-10-criteria: DF20-29: primary psychotic disorders, and DF30-39: affective disorders in the time period from 3650 days to 120 days prior to the colorectal cancer operation.

b Adjusted odds ratio (OR) with 95% confidence interval (CI).

d Missing information: 2 patients with psychiatric disorder, 119 referents without psychiatric disorder.

e CC=Colon cancer patients, RC= Rectal cancer patients.

f Intended curative treatment among colon and rectal cancer patients combined regardless of acute or not.

g Missing information: 76 (18.01%) patients with psychiatric disorder, 3,108 (12.55%) referents without psychiatric disorder.

h Oncological treatment = Received at least one oncological treatment (chemotherapy or radiotherapy), by cancer site.

i Model A: adjusted for age, gender, Charlson Comorbidity Index score.
Model B: adjusted for variables in Model A + stepwise further adjustment for cancer stage at the time of operation, socio-economic position, educational level, OR for the full model with all six adjustments provided.

However, we think that this table will be too confusing to include in an Appendix to the article. Instead we have included a sentence in the result section p12, last paragraph (line 1-8 from below): “For each of the outcomes we investigated, whether stepwise adjustment for any of the possible confounding factors: age, gender, Charlson Comorbidity Index score, the cancer stage at the time of operation, socio-economic position, and educational level had statistically significantly influenced the OR of psychiatric history. This was not the case. Removing educational level as a confounder in the model and only adjusting for five confounding factors did not change the results. Furthermore, for each of the investigated outcomes, we calculated the correlation between the estimated coefficients and we found that the highest correlation between the estimated confounders and psychiatric history was approximately 0.05.”

We have also included a sentence in the discussion, p. 15, line 5-13:

“We have included possible confounders previously mentioned in the CRC literature in the models. Educational level may to some degree be correlated with socio-economic position. We checked for each of the investigated outcomes whether stepwise adjustment for the possible confounding factors age, gender, Charlson Comorbidity Index score, cancer stage at the time of operation, socio-economic position, and educational level had statistically significantly influenced the OR. This was not the case. Furthermore, the coefficients estimates of the possible confounding factor socio-economic position and educational level was only weakly correlated (correlation coefficient approximately 0.05) to the estimate of psychiatric history. Therefore such correlations may not explain the findings.

The cancer stage was not correlated with comorbidity as defined in our study.

B2) Furthermore, estimated coefficient correlation matrix could help in evaluating the presented model. A certain degree of collinearity could be possible between the confounding variables and we therefore calculated correlation matrices of coefficients of the logit model.
REPLY:

We agree that more information is necessary regarding this issue. We have included a sentence in the analysis section page 9, line 5 from above:

We adjust for each of the possible important confounders as described in the CRC literature: gender, age and the Charlson comorbidity index score, pathological cancer stage (UICC cancer stage I-II versus III -IV) [24], socio-economic position (four levels), and educational level (three levels) in the adjusted analysis model. After each adjustment step we evaluated the corresponding OR with 95% CI.

We have included a sentence in the analysis section page 9, line 3-4 from below:

“We have analyzed the correlation between each of the possible confounders and between having had a psychiatric disorder and the confounding factors.”.

We have (as written above) included a sentence in the result section p12, last paragraph.

“For each of the outcomes we investigated, whether stepwise adjustment for any of the possible confounding factors: age, gender, Charlson Comorbidity Index score, the cancer stage at the time of operation, socio-economic position, and educational level had statistically significantly influenced the OR of psychiatric history. This was not the case. Removing educational level as a confounder in the model and only adjusting for five confounding factors did not change the results. Furthermore, for each of the investigated outcomes, we calculated the correlation between the estimated coefficients and we found that the highest correlation between the estimated confounders and psychiatric history was approximately 0.05.”

We have (as written above) included a sentence in the discussion, p. 15, line 5-13:

“We have included possible confounders previously mentioned in the CRC literature in the models. Educational level may to some degree be correlated with socio-economic position. We checked for each of the investigated outcomes whether stepwise adjustment for the possible
confounding factors age, gender, Charlson Comorbidity Index score, cancer stage at the time of operation, socio-economic position, and educational level had statistically significantly influenced the OR. This was not the case. Furthermore, the coefficients estimates of the possible confounding factor socio-economic position and educational level was only weakly correlated (correlation coefficient approximately 0.05) to the estimate of psychiatric history. Therefore such correlations may not explain the findings.

However, we think it will confuse the reader to include a table as an Appendix to the article.

Minor comments:

c) Analysis section (page 8 second paragraph): "The distribution of the cancer treatment by pre-existing psychiatric disorders status was provided". Where? Reply: We agree. We have now included in the Method, analysis section, p. 8, line 3 from below: The distribution of the cancer treatment by pre-existing psychiatric disorder status was calculated (provided in Table 3).

d) Page 10, last forth lines: The OR adjusted for age, gender, comorbidity index score, cancer stage, socio-economic position, and educational level is provided". Where? Reply: We agree. We have now included in the Result section, p. 11 last line. The OR adjusted for age, gender, comorbidity index score, cancer stage, socio-economic position, and educational level is provided: .."in Table 3".

Best regards,

Linda Kaerlev, MD, PhD