Author's response to reviews

Title: Increased health care utilization by survivors of childhood lymphoblastic leukemia is confined to those treated with cranial or total body irradiation: a case cohort study

Authors:

Anna S Holmqvist (anna.sallfors-holmqvist@med.lu.se)
Christian Moëll (christian.moell@skane.se)
Lars Hjorth (lars.hjorth@skane.se)
Anna Lindgren (anna@maths.lth.se)
Stanislaw Garwicz (stanislaw.garwicz@skane.se)
Thomas Wiebe (thomas.wiebe@skane.se)
Ingrid Øra (ingrid.ora@med.lu.se)

Version: 2
Date: 7 March 2014

Author's response to reviews: see over
To BMC Cancer

Dear Editor Dafne Solera and Reviewers,

Thank you very much for the opportunity to revise and resubmit our manuscript entitled “Increased health care utilization of survivors of childhood lymphoblastic leukemia confined to those treated with cranial or total body irradiation: a case cohort study”. We especially want to thank the reviewers for their thoughtful comments and valuable suggestions.

We think that the revised manuscript is substantially clarified and improved thanks to the reviewer’s comments, and our point-by-point responses are listed below. The changes have been entered in the revised manuscript with major and essential changes highlighted.

On behalf of all the authors,

Sincerely,

Anna Sällfors Holmqvist, MD
Pediatric Oncology and Hematology
Clinical Sciences, Lund University
SE-221 85 Lund, Sweden
Phone: +46 46 178294,
Fax: +46 46 172299
E-mail: anna.sallfors-holmqvist@med.lu.se

Ingrid Øra, MD, PhD
Assoc. Prof. / Senior Consultant
Pediatric Oncology and Hematology
Clinical Sciences, Lund University
22185 Lund, Sweden
Phone: +46-722214431
E-mail: ingrid.ora@med.lu.se
Response to reviewers

Reviewer 1

Major Compulsory Revisions - There needs to be clarification to the purpose of the study (definition of hospitalization) and how the data is presented (please see attachment)

Response:
Thank you for this important comment. We now understand that our definition of “hospitalization” and the purpose of the study were not clearly presented in the previous version. We have changed the title according to your suggestion and instead of “hospitalization” we use “hospital contact” through out the paper. “Hospital contact” is defined in the abstract and methods section.

Abstract:
- The results presented in the abstract do not support the conclusions in the abstract. The results of the abstract do not mention (or data) that hospitalizations were no different between non-irradiated and controls.

Response:
Thank you for pointing this out. The content of the abstract has been changed to support the conclusions, according to your comment. Please see revised manuscript.

- What is the “hospitalization pattern”, is this different from the # of hospitalizations?

Response:
The term “hospitalization pattern” referred to the different aspects of hospitalization (i.e., number of hospital contacts as well as the number of days in hospital). To avoid confusion, the word “hospitalization pattern” has been excluded in the revised manuscript.

Outcome variables:
- What is a ‘blanking period”? This needs to be clarified – it is mentioned in several parts of the paper.

Response:
The word “blanking period” referred to the first five years after diagnosis or relapse during which time no hospital contact was counted as an end-point. The word “blanking period” has been excluded in the revised manuscript and this approach is explained in other words.

- Why are outpatient visits included in a report on ‘hospitalization” of ALL survivors? This makes your comparisons to other studies meaningless and gives you falsely elevated rates. If you are included outpatient visits then I think your title and aim of the paper needs to be revised/clarified.

Response:
Thank you for giving us the opportunity to clarify this. We included outpatient visits, i.e. specialized care visits, because we consider this to better represent the morbidity of the study population than inpatient care alone. Since we have chosen this approach, we have now changed the title and clarified this throughout the paper by using the term “hospital contacts” instead.

- You also mention that: “If both the main and all other discharge diagnoses registered for a specific hospitalization were ALL, the hospitalization was excluded since it probably represented a routine follow-up after ALL.” Not sure you should exclude because generally ALL follow-ups (after 5 years) should not be admitted to the hospital – and may actually represent a true illness.

Response:
This is a very good point. However, in Sweden, all childhood cancer survivors are followed-up at the hospital at minimum until 18 years of age. Thus, hospital contacts without other
discharge diagnoses than ALL, as in the current study, need to be excluded when analyzing Swedish data. This has been clarified in the revised manuscript.

- Did you look at Treatment Era as a variable? This would be interesting to see (in a table) or at least comment on.
  
  **Response:**
  Thank you for raising this important question. Unfortunately, the subgroups of survivors from each treatment era are too small in the current study. However, we did analyze the impact of treatment modality, which in part could be seen as a substitute for treatment era. This limitation is added to the discussion section in the revised manuscript.

**Results**

- Table 3 should include columns for Irradiated survivors and non-irradiated survivors (in addition to all survivors and controls).
  
  **Response:**
  Changes have been made accordingly.

- Table 4 – should add columns for irradiated and non-radiated survivors.
  
  **Response:**
  We understand the reviewers point. However, the main objective of the study was to compare ALL survivors to controls. Furthermore, the small number of patients in each group of diagnosis does not allow sub-group analyses regarding type of diagnosis.

- Should have a table looking at the hospitalizations (%) by the various clinical characteristics (including treatment era).
  
  **Response:**
  This is a relevant suggestion. Hospital contacts by the most relevant clinical characteristics have been added to Table 3. To avoid too much data in the table and/or too many tables, we believe this is appropriate. If you still want the numbers regarding hospital contacts by additional clinical characteristics, we suggest that we add these numbers in a supplementary table.

- You need to be clear with your results – is there a difference in hospitalization rates between non-irradiated and controls?: “In addition, among individuals with at least one admission, ALL survivors had more admissions (3 [1–6] vs. 2 [1–4], p<0.001), and spent more days in hospital (6 [2–18] vs. 3 [1–7], p<0.001) than the controls (Table 3). When survivors treated with total body irradiation and their controls were excluded, the analyses showed comparably significant results. (page 9)” and “There was no significant difference between the non-irradiated survivors and controls regarding the risk of being hospitalized at least once, the number of days in hospital or the number of hospitalizations. (page 11)” These 2 statements seem to be in conflict – please explain or correct.
  
  **Response:**
  Excuse us for being unclear. The results of the analyses described in the first sentence were repeated excluding only the 14 patients treated with total body irradiation (TBI) in addition to chemotherapy, in order to show that the observed differences between ALL survivors and controls, reported in the first sentence, are not explained by an increased number of hospital contacts and/or days in hospital among the subgroup of survivors treated with TBI. In the second sentence, all patients treated with any radiotherapy are excluded. We have added a sentence in the first paragraph of the result section to elucidate this in the revised manuscript.

- Did the gender effect hold up within the radiation group? And in the comparison on nonirradiated and controls?
  
  **Response:**
  Yes. The observed gender difference was equally large in all subgroups of treatment modality.
Discussion:

* I don’t understand this statement - “Furthermore, the CCSS is hospital-based, while the present study is distinguished by being strictly population-based and includes outcome measures that are based on comprehensive nationwide registers.”

Response:
Again, sorry about the confuse wording. We intended to specify that our study is strictly population based as opposed to the CCSS, which relied on inclusion from selected hospitals. This has been clarified in the discussion section of the revised manuscript, paragraph 2.

* “In contrast to both these studies, we found an increased risk of hospitalization only in the subgroups of survivors whose treatment included radiotherapy in addition to chemotherapy.” This is the crux of your paper and I cannot find the actual rates (%) or comparison numbers for the irradiated group – this need to be more clearly stated (probably in a table).

Response:
Thank you for pointing this out. According to your comment, we have included the actual rates for the patients treated with CRT and TBI, respectively, in Table 3.

* In the discussion you mention that life threatening conditions (pg 13) in your results are comparable to the CCSS study – this data is not mentioned. How was this measured? This should be discussed in the methods and described in the results sections.

Response:
The aim of this sentence was to describe the conclusion in the CCSS paper; that the majority of non-irradiated, non-relapsed ALL survivors did not have an increased morbidity. We have now omitted the misleading sentence and changed the wording to make it clearer (discussion section, paragraph 5).

* “The limitations of the current study must be considered. The Swedish National Hospital Register includes hospital-based outpatient data only since 2001, and no data from general practitioners are included, so the present study mainly captures conditions resulting in admission to hospital.” I don’t understand this statement. Isn’t this the purpose of your study to look at ‘hospitalization’ admissions – if not this needs to be clarified from the beginning as the title of the paper would be misleading? If ‘hospitalizations’ is going to include outpatient visits, the terminology will need to change (change title) to ‘health care utilization’ or something like that.

Response:
We have now changed the terminology in the paper and the title according to this essential suggestion.

Reviewer 2

- Major Compulsory Revisions
1. Background; Paragraph 4: State your aims more detailed and clearly and address each of your aim in the analysis part and the results part. In the current status it is difficult to follow the results because from the background and analysis part it is not yet clear what you analysed and investigated.

Response:
Thank you for identifying this error. We agree with the reviewer. We have now structured the last paragraph in the background section, the statistical analyses section, the result and discussion section in the same order to improve readability.

2. Background; Paragraph 4: You aimed to analyse factors for morbidity for health care
planning of ALL survivors. While you show the risk factors for morbidity in the results section, you don’t interpret these findings in the discussion regarding your aim on health care planning and implementations into practice.

Response:
Thank you for pointing this out. A sentence discussing the translation of our results is now added to the discussion section, now paragraph 5.

3. Methods; Outcome variables; Paragraph 1: The Swedish Hospital Register has been a national register only since 1987 and it includes outpatient visits only from 2001 onwards. You also acknowledge this as a limitation in your discussion. Have you done some sensitivity analyses where you include only patients diagnosed later than 5 years prior to 1987 and 2001, respectively? Making such a sensitivity analysis and shortly stating the results might strengthen your paper. If you choose not to make a sensitivity analysis, please state in your limitations section, how this problem could affect your results.

Response:
Since there are significant differences in treatment modality during the study period, with cranial irradiation being much more common in the earlier years, and since the follow-up time of these differently treated survivors differ (Table 1), we have chosen not to make such sensitivity analysis. According to this valuable comment, we have added a statement regarding this in the limitation section.

4. Methods; Outcome variables; Paragraph 3: How sure can you be that the increased hospitalizations are not due to routine follow-up visits? Can you give the reader an impression on that? Have you asked some clinicians, what they note in the discharge reports of follow-up visits? If you cannot rule out the possibility that a part of the increased hospitalizations may be due to routine follow-up visits, please acknowledge this in the limitations part of your discussion.

Response:
We understand that this can be interpreted as a potential limitation. However, by excluding all hospital contacts without other diagnoses than ALL, we believe that we have excluded the absolute majority of routine follow-up visits. All but two of the co-authors are senior consultants in pediatric oncology and the way of diagnosing routine follow-up visits is similar in the whole country. In addition, if a significant amount of routine follow-up visits were included in the material, an increased number of hospital contacts also among non-irradiated survivors should have been seen.

5. Methods; Statistical analyses: Please rewrite this section step by step corresponding to your aims and results. There is no description of the analysis to compare survivors with and without irradiation and controls. The identification of risk factors for hospitalizations is also not described clearly enough: please describe all the models you performed to get to your results. At the moment it is difficult to follow your results based on the analyses steps given.

Response:
Thank you for this very relevant remark. Changes in the section of statistical analyses have been made accordingly.

6. Methods; Statistical analyses; Paragraph 1: Please explain, why you transformed your outcomes (number of hospitalizations and number of days in hospital) from a continuous to a binary variable. You lose a lot of information by doing this.

Response:
From a clinical perspective, the factor that has the most impact is if there has been few or many numbers of hospital contacts and if there has been short, intermediate or long time in hospital. The absolute number of hospital contacts or the exact duration of the hospitalization is of less importance, since it varies a lot depending on type of illness and doesn’t necessary reflect the severity of the illness. In addition, the distribution of number of hospital contacts and days in hospital was very skewed.

7. Methods; Statistical analyses; Paragraph 2: In your analyses on factors associated with your
outcomes you write about an ordinal logistic regression for the number of hospital admissions, but the outcome “hospital admissions” was not defined as categorical variable before. The reader does not know how the outcome exactly looks like.

Response:
We are sorry about this. By mistake, we used two different words for an outcome. We have changed the wording in the revised manuscript.

8. Methods; Statistical analyses; Paragraph 2: You say that you use random-effects for the clusters of cases and controls. Does that mean, that you performed a multilevel logistic regressions? If so, please name it like that at the beginning of the paragraph. If you have done something else, please describe it shortly.

Response:
We performed multilevel logistic regressions and have now changed the paragraph in the statistic section, describing this more clearly.

9. Results; Hospitalization rate and diagnoses; Paragraph 1: Show these results additionally stratified for those with cranial irradiation, total body irradiation and not-irradiated patients. Add these numbers in Table 3 or in a separate Table.

Response:
Changes have been made to Table 3 according to comment.

10. Results; Risk factors for hospitalization: Show the results for this section in a Table! Show also the adjusted OR for being hospitalized comparing survivors and controls. Distinguish this paragraph between factors associated with hospitalizations overall and differences of risk factors between survivors and controls. Show also the results of interaction terms in your table if you used this to assess differences in risk factors between survivors and controls. Write this paragraph in accordance to the newly written analysis steps.

Response:
Thank you for this valuable comment. The adjusted OR and the interaction terms are now shown in a separate Table 6. The corresponding paragraph in the result section has been changed accordingly.

11. Results; Risk factors for hospitalization; Paragraph 2: You always say that those ALL survivors not treated with irradiation did not show increased hospitalization rates but you never actually show these results. I would re-analyse the data of Table 5 taking only the controls as baseline and showing the risk for non-irradiated ALL survivors, ALL survivors with cranial irradiation and ALL survivors with total body irradiation. Based on these results you can state your conclusion.

Response:
Thank you, again, for a valuable comment. The data of Table 5 has been re-analysed according to your suggestion.

12. Discussion; Paragraph 3: You explain the differences in pulmonary diagnoses between your study and references 14 and 16 because of different smoking habits between survivors and controls. But this behaviour would also count for references 14 and 16 and could not explain the difference between them and your study, just the difference within your study.

Response:
We agree that this is likely to be the case. Changes have been made according to your comment in the revised manuscript.

13. Discussion: Add some clinical implications that might result from your study!

Response:
The clinical implications of our study are now discussed in the revised manuscript, paragraph 5 of the discussion section.
- Minor Essential Revisions

1. Abstract; Results: Add units for the frequency of admissions (3 days per month, days per year?).
   **Response:**
   Changed according to comment in the revised manuscript.

2. Abstract; Results: Add the proportion of survivors with total body irradiation as done for those treated with cranial irradiation.
   **Response:**
   Changed according to comment in the revised manuscript.

3. Abstract; Results: The conclusion on not difference between non-irradiated ALL survivors and controls was not shown before in the results of the abstract. Please add these results in the abstract or delete this part of the conclusion in the abstract.
   **Response:**
   Changed according to comment in the revised manuscript.

4. Background; Paragraph 3: I would focus the background literature more on ALL patients only since this is the population of your paper. Point out more clear what is known in ALL patients and what are the limitations in the literature making your study important.
   **Response:**
   We agree that this improves the manuscript. Changes according to the comment have been made in the revised manuscript.

5. Results; Hospitalization rate and diagnoses; Paragraph 1: Add units for your numbers of admissions and days in hospital.
   **Response:**
   Changed according to comment.

6. Discussion; Paragraph 6: You explain conflicting findings regarding risk for hospitalization of males and females because of gender differences in cancer survivors and controls. This sentence is not clear for me.
   **Response:**
   We are sorry about the confusion. Changes have been made in the revised manuscript to improve clarity, now in paragraph 6.

7. Table 1: Please indicate for each variable whether you used row or column percentages. For example for relapse and cranial irradiation numbers do not sum up to 100%. Please add a column with the total of all survivors and give a p-value for differences between the three populations (chemotherapy only; CRT; TBI).
   **Response:**
   Table 1 has now been revised according to comment to clarify that we’ve used column percentages. A column with the total of all survivors is also added. The differences between the populations in Table 1 are very large due to changes in treatment regimes during the time period studied. The data in Table 1 is merely for descriptive purposes and not a hypothesis tested per se. Therefore, we have chosen not to add p-values for the differences between the three populations.

8. Table 2: Please add a p-value for differences between survivors and controls. The numbers in the two education variables do not add up to 100%.
   **Response:**
   We are sorry for not including the “missing” data. This mistake is now corrected and the two education variables now add up to 100%. P-values have been added according to comment.

9. Table 3: Are the number of hospitalizations per year or over the whole period?
Please indicate a unit. Are the numbers of days in hospital per each hospitalization or overall? Please add a unit.

**Response:**
Units are added according to comment.

- Discretionary Revisions

1. Results; Hospitalization rate and diagnoses: I would split the two topics up with two separate subtitles, one for the hospitalizations and one for the diagnoses.

**Response:**
Changed according to comment.

2. Results; Hospitalization rate and diagnoses; Paragraph 2: You could add some numbers for the diagnoses in this paragraph.

**Response:**
It may be preferable, but according to author guidelines, tables and texts should be complementary and we therefore leave the text as it is.

3. Discussion; Paragraph 5: You could add some hypotheses, why the irradiated patients might have higher morbidity regarding the diagnoses you found to be prominent among ALL survivors.

**Response:**
We agree that this would be of great interest and it may be a logical next step for future studies. However the present study is neither designed nor powered to explore the mechanisms behind the observed associations. Any such hypothesis would therefore be purely speculative at this point.

4. Discussion: I would add some strengths of your study!

**Response:**
Thank you for your encouragement! Please see second paragraph in the discussion section of the revised manuscript.