ARTICLE DETAILS

<table>
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<th>TITLE (PROVISIONAL)</th>
<th>Long-Term Time Trends in Incidence, Survival, and Mortality of Lymphomas by Subtype among Adults in Manitoba, Canada: A Population-based Study using Cancer Registry Data</th>
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<tr>
<td>AUTHORS</td>
<td>Ye, Xibiao; Mahmud, Salaheddin; Skrabek, Pamela; Lix, Lisa; Johnston, James</td>
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GENERAL COMMENTS

This article describes temporal trends in incidence, mortality and survival of lymphoma among adults in Manitoba, Canada. A major strength of these descriptive data is that trends are reported by subtype as NHL subtypes are typically reported as one single entity which does not reflect the heterogeneity in both incidence and survival from lymphoma. The paper is generally well-written, and the statistical methodology used is appropriate. I have some comments with respect to the methodology, these should be regarded as minor and most just need some clarification.

On page 8 the authors describe that the Ederer method was used to calculate expected survival. My guess is that they refer to the Ederer II method (gold standard these days) and not the Ederer I method. This should be clarified.

For the age-specific estimates of RS in HL patients it would be more informative to present the estimates in 4 age groups (split the youngest age group into two) due to the peak in incidence around age 25-30, and the fact that previous research suggest that HL among young are likely to be biologically different from HL in the elderly.

The authors describe that they have applied period analysis to their survival estimates. From the description of the software package they use, as well as from the references it appears that they really are doing that, however, there is no description of what period window was used. Also, the RS survival estimates seem to come from a full cohort analysis, i.e. I found no results in the tables and figures that present the period estimates of survival for recently diagnosed patients (however that was defined via the period
window). This needs to be clarified in the methods section as well as the results section.

The trend showing an increasing incidence of total NHL among females is interesting as the increase persists until 2001, as opposed to the mid-1990s which has been reported elsewhere previously. Do the authors have any explanation for the difference (comparing males to females)?

In the results section, the paragraph referencing the APC-results, needs to be checked as the figure references are not correct.

In the limitations section of the discussion the authors discuss net survival versus survival estimated in the presence of competing risks. I suggest that these sentences are removed (starting with "However, the current approach is based on", and finishing with references 64-65). Firstly, the first sentence would be more informative if the authors made it clear that they refer to "net survival". I.e. these presented survival analyses basically assume two things, that deaths from lymphoma is independent of deaths from other causes (conditionally on the covariates included in the models). This is the "independence assumption". Furthermore the other key assumption is that the lymphoma patients are exchangeable to the background population, i.e. that the observed all-cause mortality of the patients would have been similar to that of the general population had the patients not been diagnosed with lymphoma. If these assumptions are both true then RS can be interpreted as net survival. That is, the RS estimates show what the survival would look like if lymphoma was the only possible cause of death. Net survival is precisely the quantity of interest for an investigation like this as we don’t want our temporal trends to be influenced by deaths due to other causes. So if the assumptions above are satisfied this is a strength of the study, rather than a limitation.

Survival estimated in the presence of competing risks is really only relevant if the interest is in quantifying trends in what proportion of patients "actually" die from lymphoma, i.e. whilst taking into account that some will die from other causes first. Such trends may look very different and could simply reflect changes in the distribution of deaths due to other causes over time, thereby making them less relevant as basis for cancer control activities (i.e. understanding the impact of new diagnostic tools or treatments etc etc on survival).

It is true that our group has developed methods for estimating statistical cure as well as survival in the presence of competing risks in a flexible parametric survival framework (refs 64-65). However, the paper where the two strategies were combined is in fact:

"The application of cure models in the presence of competing risks: a tool for improved risk communication in population-based cancer patient survival.", published in Epidemiology in 2014 by myself, Dickman and Lambert et al.

However, for the purposes of this investigation the methodology presented in that paper is less relevant as the correct approach has already been used, i.e. estimation of net survival. Therefore I think that referencing these three papers does not add much to the current investigation, although an interesting next step might be to study how these changes in net survival translate to the "real-world"
probability of dying from lymphoma. For this purpose all three references would be useful.

In table 1, I recommend that the authors double check the N for males and females. There seems to be 1 person too much in the male column and one person missing among the females for the numbers to add up (by subtype).

In the footnote of Table 2, please add information about the source of the p-value. Joinpoint models? What was the test?

Table 3: I was not familiar with the EAPC and AAPC measures. The AAPC measure is well-described on the NCI website but I couldn’t find information about the EAPC. I think it would be useful if the distinction between these measures was described briefly in the methods section. For example, it is not recommended to use the AAPC to compare groups if the calendar periods are not identical. The authors have not done that for the AAPC, but they have for the EAPC (males vs females NHL) so I was wondering if this is a valid approach?

**GENERAL COMMENTS**

Ye at al. present an analysis of lymphoma incidence, mortality, and relative survival, based on data from the Canadian Manitoba cancer registry, 1984-2013. The main findings are that the NHL incidence increased until 2000, followed by a steady rate, paralleled by increased and decreased mortality around similar timepoints, as well as ongoing decline in Hodgkin lymphoma mortality.

The analysis is very straightforward, the authors are commended for the use of modern epidemiology tools, including joinpoint regression for trend analysis and decomposition of trends in age-cohort-period models with the use of RCS for non-linear effects. I have no major concerns regarding the methodology.

The weakness of the study is that it largely recapitulates findings from other, larger studies from Europe and the US, without any locale-specific phenomena that could elucidate the reasons for changes in incidence, mortality, or survival. Most of the trends presented are difficult to understand. For example, major treatment advances in HL have been largely confined to the younger population, so it is hard to understand why it is the older patients that have the largest increase in survival. The putative reason for a sudden decrease in CLL incidence is also unexplained. The most perplexing are the effects of cohort on incidence and mortality, which appear large, but without any explaining factors. The authors discuss some differences compared with the USA or Europe, but without the context of lead-time bias specific to diagnostic patterns, which can significantly affect incidence and survival rates. Without such context and interpretation, it is hard to discern statistical noise from important phenomena.

Additional minor comments for the discussion:
• The authors should consider the effect of changing diagnostic practices on the incidence and survival, particularly changes in the diagnostic criteria for myeloma, CLL – as related e.g. to the availability and increased use of flow cytometry (see Seftel et al., Leuk Res. 2009).
• The HIV epidemic had impact on the incidence and mortality of certain subtypes of NHL (DLBCL, Burkitt) in the 1990’s – as previously evaluated by Shiels et al., CEBP 2013. Has this been recorded by the Manitoba registry?
• The large survival gains in FL are commonly ascribed to the introduction of rituximab, and disparities in these trends were noted e.g. in Europe (Mounier et al., Lancet Haematol. 2015). Can the authors comment on the timing of introduction of rituximab in Manitoba in this context?
• Several citations need adjustment and renumbering. For example, P13 L276 – Ref. 39 is from a Dutch registry, not from the USA; P15 L342, Ref. 37 does not concern NHL mortality.
• The results section repeats a lot of numbers from the Tables. Table 5 for example is nearly completely duplicated in the text, which could be more focused and selective.

REVIEWER
Yong-Bing Xiang
Shanghai Cancer Institute, China

GENERAL COMMENTS
Xibiao Ye and his colleagues conducted a data analysis on the 30 years time trends in incidence, survival and mortality of lymphomas in Manitoba, Canada. I think it is an interesting study, as well as an important data for further analytic epidemiological studies.

Minor revision
Some minor suggestions or/and comments are as follows:
1. Lines 50-51: Please check the conclusion of “Survival improvements and mortality reductions were seen for all major subtypes in both sexes.” I think it is overstated for the “mortality”. Because as shown in table 7 and text of Lines 361-362, the author did not test the time trends in mortality for most NHL subtypes.
2. Line 112: I am just wandering the time period of 2006-2010 in the statement of “Most cases are pathologically confirmed (94% for cases registered between 2006-2010).” Because incidence cases diagnosed between 1984 and 2013 were analyzed in this paper. Why did the author select this time period (2006-2010), and why not other time period ?
3. Line 132-133: The author used the 2006 population of Canada from Canadian Census as the standard population. And compare the time trends with the USA, Japan, or Europe data in Discussion Part. To better compare the international Incidence or mortality, my suggestion is using the world population as the standard population.
4. Line 185: The “HL and NHL accounted for 6.1% and 87.7% of total lymphomas, respectively” seems just for males ? If so, please revise it.
5. Lines 186-187: The authors need to check the percentage 95% in the sentence of “Over 95% of HL cases were classical HL” ? Because, for males, it is 94.0%, and 97.5% in females.
6. Line 193: Please check the range of age-standardized incidence rates for total HL in females (2.2-2.8) ? According to the results of Table 2, it is 2.9 per 100,000 during 1984-1989.
7. Line 209: Please check the word of “FCN” in the sentence of “FCN incidence remained relatively stable in both sexes.” It should be “PCN” ? Moreover, this conclusion is not correct. According to the results of Table 3 and Table 7, AAPC of PCN for the full period (1981-2013) is 0.6 (0.1-1.2), which shows the PCN incidence increased slightly, not stable, in this study ?
8. Line 216: The authors need to check the age groups of "85 years and then declined (Figure 2a and 2b)". It is 85 or 80? as well as that in Figure 2a and 2b or Figure 1c and 1d?
9. Line 218: "Figures 2g and 2h". Please check it. Is it Figure 1g and 1h?
10. Lines 221-222: The authors stated that "Incidence for the other NHL subtypes started to decline among those born since 1950s, although the changes are not statistically significant." But according to the Figure 1g and 1h, incidence of CLL/SLL in the males continuously declined among those born since 1950s. And incidence of PCN in the females increased?
11. Lines 238-239: Please change the figures in the sentence of "Age-standardized mortality for NHL was 16.58 in males and 13.71 in females". For example, you may change 16.58 to 16.58 per 100,000.
12. Lines 242-244: I did not see any tables or figure to support this result? Please clarify it.
13. Lines 247-253: The description of this paragraph is not consistent with the results of Table 6. For example, 5-year relative survival rates for female CLL/SLL are not decreased with age, which is not consistent with the statement in the "In both males and females, 5-year relative survival for NHL subtypes decreased with age". For female CLL/SLL, relative survival significantly decreased in those aged 20-54 years, which is not consistent with "For CLL/SLL, relative survival has been stable over time in those aged 20-54 years". Considering sex difference in 5-year relative survival, please check this description or statement.
14. Lines 256-260: Considering sex difference for age-standardized 5-year relative survival, my suggestion is to describe the results by male and female here, separately.
15. Table 1: The total number of LN in the males is 6808, but the total of all the subtype of LN in the males is 6809? Please check it.
16. Table 1: if "NHL, B-cell, NOS" is one subtype of mature NHL, B-cell so the position of "NHL, B-cell, NOS." should align with the PCN?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
On page 8 the authors describe that the Ederer method was used to calculate expected survival. My guess is that they refer to the Ederer II method (gold standard these days) and not the Ederer I method. This should be clarified.

"the Ederer II method" is now specified.

For the age-specific estimates of RS in HL patients it would be more informative to present the estimates in 4 age groups (split the youngest age group into two) due to the peak in incidence around age 25-30, and the fact that previous research suggest that HL among young are likely to be biologically different from HL in the elderly.

We agree with the reviewer that HL incidence has an unusual bimodal age distribution (i.e., two peaks around ages 20-24 and 80-84), which is also shown in the present analysis. However, analysis based on 4 age groups will generate unstable estimates of relative survival or the model would not converge due to a small sample size. We have revised age categories to 20-29, 30-54, and 55+ years for HL RS analysis in order to show potentially different patterns in young patients.

The authors describe that they have applied period analysis to their survival estimates. From the description of the software package they use, as well as from the references it appears that they
really are doing that, however, there is no description of what period window was used. Also, the RS survival estimates seem to come from a full cohort analysis, i.e. I found no results in the tables and figures that present the period estimates of survival for recently diagnosed patients (however that was defined via the period window). This needs to be clarified in the methods section as well as the results section.

The results for the period estimates of relative survival have been included as supplemental table (table S3) and described in the main text, lines 262-267. “Differential period effects were found for HL and NHL and major subtypes (Supplemental Table S3). Comparing to 1984-1993, relative excess mortality risk for HL in both sexes was similar in 1994-2003 and 2004-2013; a statistically significant period effect was only seen in 2004-2013. Period effects were observed in 2005-2013 only for NHL subtypes with an exception of CLL/SLL. Statistically significant period effects were found for CLL/SLL in both 1994-2003 and 2004-2013.”

The trend showing an increasing incidence of total NHL among females is interesting as the increase persists until 2001, as opposed to the mid-1990s which has been reported elsewhere previously. Do the authors have any explanation for the difference (comparing males to females)?

There are no uniformed time trends in NHL incidence across countries, although a few studies showed that the incidence increased until mid 1990s (Bosetti et al). However, later studies have showed that NHL incidence persistently increased after mid-1990s in some areas. For example, in Nordic Countries, NHL incidence in females continuously increased by 0.7% annually during 1994-2003 (Sandin et al 2006). In Shanghai, China, NHL incidence in females persistently increased by 2.5% annually during 1973-2010 (Bao et al, 2016). We have revised the statement on previous findings on NHL incidence time trends in the Background section as follows (lines 75-76):

“Over NHL incidence persistently increased prior to mid 1990s globally.1-4 Time trends thereafter diverged (i.e. incidence continuously increased in some countries such as USA5,6 but declined in other areas2,3).”

In the results section, the paragraph referencing the APC-results, needs to be checked as the figure references are not correct.

This section has been revised accordingly.

In the limitations section of the discussion the authors discuss net survival versus survival estimated in the presence of competing risks. I suggest that these sentences are removed (starting with "However, the current approach is based on", and finishing with references 64-65). Firstly, the first sentence would be more informative if the authors made it clear that they refer to “net survival”. I.e. these presented survival analyses basically assume two things, that deaths from lymphoma is independent of deaths from other causes (conditionally on the covariates included in the models). This is the “independence assumption”. Furthermore the other key assumption is that the lymphoma patients are exchangeable to the background population, i.e. that the observed all-cause mortality of the patients would have been similar to that of the general population had the patients not been diagnosed with lymphoma. If these assumptions are both true then RS can be interpreted as net survival. That is, the RS estimates show what the survival would look like if lymphoma was the only possible cause of death. Net survival is precisely the quantity of interest for an investigation like this as we don’t want our temporal trends to be influenced by deaths due to other causes. So if the assumptions above are satisfied this is a strength of the study, rather than a limitation. Survival estimated in the presence of competing risks is really only relevant if the interest is in quantifying trends in what proportion of patients “actually” die from lymphoma, i.e. whilst taking into account that some will die from other causes first. Such trends may look very different and could simply reflect changes in the distribution of deaths due to other causes over time, thereby making them less relevant as basis for cancer control activities (i.e. understanding the impact of new diagnostic tools or treatments etc on survival).

It is true that our group has developed methods for estimating statistical cure as well as survival in the presence of competing risks in a flexible parametric survival framework (refs 64-65). However, the paper where the two strategies were combined is in fact:

"The application of cure models in the presence of competing risks: a tool for improved risk
communication in population-based cancer patient survival.

According to the reviewer’s suggestions, we removed the discussions on competing risk and cure fraction. We added discussions on methodological strengths and limitations of the method (Ederer II) used in the present study (lines 383-384).

In table 1, I recommend that the authors double check the N for males and females. There seems to be 1 person too much in the male column and one person missing among the females for the numbers to add up (by subtype).

The number of “Composite HL and NHL” in males should be 2 instead of 3. The typo has been fixed.

In the footnote of Table 2, please add information about the source of the p-value. Joinpoint models? What was the test?

The note “P value, for the comparison between males and females based on the Mantel-Haenszel method.” has been added.

Table 3: I was not familiar with the EAPC and AAPC measures. The AAPC measure is well-described on the NCI website but I couldn’t find information about the EAPC. I think it would be useful if the distinction between these measures was described briefly in the methods section. For example, it is not recommended to use the AAPC to compare groups if the calendar periods are not identical. The authors have not done that for the AAPC, but they have for the EAPC (males vs females NHL) so I was wondering if this is a valid approach?

Joinpoint analysis calculates annual percentage change for each jointed period (EAPC) and the average of the EAPCs over the entire time period. The difference is described in the Methods section (line 138-140). We are trying to showcase that time trends are different (qualitatively) between males and females but no formal statistical comparisons have been conducted. Text has been revised as follows to avoid the confusion.

“The extent of the increase was in the range of changes reported in other counties. Different time trends were also found for FL, i.e., there were no statistically changes in either sex in the present study, while in the same time period FL incidence in the USA males and females declined by 2.1% annually. PCN incidence increased in males only in the present study and in USA as well.”

Reviewer: 2

The weakness of the study is that it largely recapitulates findings from other, larger studies from Europe and the US, without any locale-specific phenomena that could elucidate the reasons for changes in incidence, mortality, or survival. Most of the trends presented are difficult to understand. For example, major treatment advances in HL have been largely confined to the younger population, so it is hard to understand why it is the older patients that have the largest increase in survival.

There are two important aspects regarding age difference in HL relative survival (RS): (1) at any given time, young HL patient have higher RS than old patients; (2) relative change in RS was greater in old patients than in young patients. The findings in the present study were consistent with that from some of previous studies. For example, 5-year RS for Sweden HL patients aged 19-35 years increased from 72% in 1973-79 to 96% in 2001-09 (with an absolute increase 24% and a relative increase ratio 1.3), but that for patients aged 66-80 years increased from 18% to 44% (with an absolute increase 26% but a relative increase ratio 2.4). The data
suggest a larger relative increase in old patients than in young patients. We have revised the discussion accordingly (lines 326-333).

The putative reason for a sudden decrease in CLL incidence is also unexplained.

The following discussion has been added to partially explain the decline (lines 289-291):

“The reduction in CLL/SLL incidence may be explained by the diagnosis change, i.e., individuals who would have been classified as CLL/SLL were classified as monoclonal B-cell lymphocytosis (MBL) if the absolute B-cell count was < 5 × 10^9/L.”

The most perplexing are the effects of cohort on incidence and mortality, which appear large, but without any explaining factors. The authors discuss some differences compared with the USA or Europe, but without the context of lead-time bias specific to diagnostic patterns, which can significantly affect incidence and survival rates. Without such context and interpretation, it is hard to discern statistical noise from important phenomena.

The following statement has been added (lines 371-372):

“Lead time bias associated with better diagnostic techniques e.g. flow cytometer might have also played a role.”

Additional minor comments for the discussion:

• The authors should consider the effect of changing diagnostic practices on the incidence and survival, particularly changes in the diagnostic criteria for myeloma, CLL – as related e.g. to the availability and increased use of flow cytometry (see Seftel et al., Leuk Res. 2009).

Discussion on this issue has been added as follow (lines 314-317):

“An earlier study in Manitoba showed a large increase in CLL/SLL incidence during 1998-2003 that was largely related to the introduction of flow cytometer testing but was also due to the misclassification of CD5 positive chronic lymphoproliferative disorders as CLL/SLL.”

• The HIV epidemic had impact on the incidence and mortality of certain subtypes of NHL (DLBCL, Burkitt) in the 1990’s – as previously evaluated by Shiels et al., CEBP 2013. Has this been recorded by the Manitoba registry?

To our best knowledge, the effect has not been examined in Manitoba. It is doable to link cancer registry to other medical databases to ascertain HIV status. But we do not have an appropriate ethical approval for accessing HIV laboratory test and diagnosis data. This analysis could be included in future research.

• The large survival gains in FL are commonly ascribed to the introduction of rituximab, and disparities in these trends were noted e.g. in Europe (Mounier et al., Lancet Haematol. 2015). Can the authors comment on the timing of introduction of rituximab in Manitoba in this context?

The following discussion has been added (lines 344-347):

“Rituximab was introduced to Europe in 1997 and to Manitoba in 2003. Survival increases were found in the present study and in Europe. The increase in FL and DLBCL survival varied between European countries, probably associated with the different introduction of rituximab to those countries.”

• Several citations need adjustment and renumbering. For example, P13 L276 – Ref. 39 is from a Dutch registry, not from the USA; P15 L342, Ref. 37 does not concern NHL mortality.

The errors have been fixed. The right country (the Netherlands) and the right reference (ref. 14) are now cited.

• The results section repeats a lot of numbers from the Tables. Table 5 for example is nearly completely duplicated in the text, which could be more focused and selective.

Text has been revised to avoid the duplication of numbers in the Table. For Table 5, the original text has been changed to:
The time trends in NHL mortality (Table 5) were different from that in HL: Total NHL mortality rates increased by 4.4% annually in males and by 3.2% annually in females by the end of 1990s; and declined thereafter in both males (by 3.6% annually) and females (by 2.5% annually).”

Reviewer: 3
Some minor suggestions or/and comments are as follows:

1. Lines 50-51: Please check the conclusion of “Survival improvements and mortality reductions were seen for all major subtypes in both sexes.” I think it is overstated for the “mortality”. Because as shown in table 7 and text of Lines 361-362, the author did not test the time trends in mortality for most NHL subtypes.

   The text has been changed to “Survival improvements and mortality reductions were seen for HL and NHL in both sexes”.

2. Line 112: I am just wandering the time period of 2006-2010 in the statement of “Most cases are pathologically confirmed (94% for cases registered between 2006-2010).” Because incidence cases diagnosed between 1984 and 2013 were analyzed in this paper. Why did the author select this time period (2006-2010), and why not other time period?

   Cancer registration in Manitoba is audited routinely. The assessment results for 2006-2010 were cited as this is the most recent report the authors could access while developing this study.

3. Line 132-133: The author used the 2006 population of Canada from Canadian Census as the standard population. And compare the time trends with the USA, Japan, or Europe data in Discussion Part. To better compare the international Incidence or mortality, my suggestion is using the world population as the standard population.

   We agree with the author that world standard population needs to be used for rate comparison internationally. But the comparisons in the Discussion section focus on time trends in Canada other than incidence/mortality rates.

4. Line 185: The “HL and NHL accounted for 6.1% and 87.7% of total lymphomas, respectively” seems just for males? If so, please revise it.

   Revised accordingly.

5. Lines 186-187: The authors need to check the percentage 95% in the sentence of “Over 95% of HL cases were classical HL”? Because, for males, it is 94.0%, and 97.5% in females.

   The sentence has been changed to “About 95% (94% in males and 97.5% in females) of HL cases were classical HL.”

6. Line 193: Please check the range of age-standardized incidence rates for total HL in females (2.2-2.8)? According to the results of Table 2, it is 2.9 per 100,000 during 1984-1989.

   The typo has been fixed.

7. Line 209: Please check the word of “FCN” in the sentence of “FCN incidence remained relatively stable in both sexes.” It should be “PCN”? Moreover, this conclusion is not correct. According to the results of Table 3 and Table 7, AAPC of PCN for the full period (1981-2013) is 0.6 (0.1-1.2), which shows the PCN incidence increased slightly, not stable, in this study?

   The sentence has been changed to “PCN incidence increased by 0.6% annually in males but remained stable in females.”

8. Line 216: The authors need to check the age groups of “85 years and then declined (Figure 2a and 2b)”. It is 85 or 80? as well as that in Figure 2a and 2b or Figure 1c and 1d?
The sentence has been changed to “Age-specific incidence rate for total NHL reached the highest at the age of 80-85 years and then declined (Figure 1c and 1d).”

9. Line 218: “Figures 2g and 2h”. Please check it. Is it Figure 1g and 1h?

Revised accordingly.

10. Lines 221-222: The authors stated that “Incidence for the other NHL subtypes started to decline among those born since 1950s, although the changes are not statistically significant.” But according to the Figure 1g and 1h, incidence of CLL/SLL in the males continuously declined among those born since 1950s. And incidence of PCN in the females increased?

This statement has been deleted. Figure 1g and 1h show a trend of declined incidence among those born after 1950s, but the changes are not statistically significant (please refer the confidence interval lines). Neither were there changes for PCN.

11. Lines 238-239: Please change the figures in the sentence of “Age-standardized mortality for NHL was 16.58 in males and 13.71 in females”. For example, you may change 16.58 to 16.58 per 100,000.

To avoid the redundancy, we specify the unit of rate the first time it appears and in the table/figure titles.

12. Lines 242-244: I did not see any tables or figure to support this result? Please clarify it.

Compared to the reference year (i.e., 2001), mortality rate ratio for NHL in males (figure 2c) was lower than 1, but increased with the time (year). The 95% CI upper limit line reaches 1 in 1995. The upper limit line started to be less than 1 in 2003.

13. Lines 247-253: The description of this paragraph is not consistent with the results of Table 6. For example, 5-year relative survival rates for female CLL/SLL are not decreased with age, which is not consistent with the statement in the “In both males and females, 5-year relative survival for NHL subtypes decreased with age”. For female CLL/SLL, relative survival significantly decreased in those aged 20-54 years, which is not consistent with “For CLL/SLL, relative survival has been stable over time in those aged 20-54 years”. Considering sex difference in 5-year relative survival, please check this description or statement.

The statement on age effect has been changed to “In both males and females, 5-year relative survival for total HL, total NHL, and NHL subtypes decreased with age except for CLL/SLL”.

The statement on CLL/SLL time trend has been changed to “For CLL/SLL in males, relative survival has been stable over time in those aged 20-54 years, but significantly improved in the older people; while in females relative survival declined over time for the youngest age group.”

14. Lines 256-260: Considering sex difference for age-standardized 5-year relative survival, my suggestion is to describe the results by male and female here, separately.

Revised as suggested and the findings are described as follows (lines 256-259):

“The trend analysis showed an overall increase in 5-year relative survival for HL and NHL (Table 6): from 1984-1993 to 2004-2013, there were 12.3% unit increase in males and 14.3% unit increase in females for HL; 11.7% unit increase in males and 7.8% unit increase in females for NHL.”

15. Table 1: The total number of LN in the males is 6808, but the total of all the subtype of LN in the males is 6809? Please check it.

The number for Composite HL and NHL in males was entered incorrectly. Revised accordingly.
16. Table 1: if “NHL, B-cell, NOS” is one subtype of mature NHL, B-cell so the position of “NHL, B-cell, NOS.” should align with the PCN?

Revised accordingly.

VERSION 2 – REVIEW

| REVIEWER | Sandra Eloranta  
| Clinical Epidemiology unit, Department of medicine, Karolinska Institutet, Sweden |
| REVIEW RETURNED | 13-Jan-2017 |
| GENERAL COMMENTS | The authors have answered all my comments except one, where I believe there is a misunderstanding with respect to the statistical methodology used. 

In the methods section the authors describe that they have used a period approach to estimating relative survival. However, in order to do a period analysis one has to define a period window (typically a calendar period window including the 3 to 5 years most recent years of the study period, in this example the latest period 2005-2013 could be an option, although this would be considered a relatively wide period window). After having selected a period window a relative survival estimate (eg 5-year) based on person-time during that window only can be calculated. I.e. period analysis is essentially a left truncated survival analysis. Thus individuals who never enter that calendar window don’t contribute to the analysis at all. This is why period analysis can yield up-to-date estimates of relative survival. It is of course also possible to produce model-based period estimates, i.e. model excess mortality using a period approach.

However, by taking this classical approach, one would not get estimates of excess mortality for calendar years that are not encompassed by the pre-specified period window, specifically the results do not show period estimates of the “5-year relative survival” by calendar period. Because the authors report excess mortality rate ratios for the full study period (subdivided into 3 categories) I suspect that no period window has been assigned and that the reported results (supplemental table 3) are in fact just excess mortality rate ratios comparing the different calendar periods.

Unless the authors have used a hybrid approach to period analysis (if so, this should be specified and the period window should be reported).

The authors should confirm what method has been used, provide a full description of the period window in the method section. If the results are indeed excess mortality rate ratios without a period approach the authors need to modify teh methods section and also modify the strengths and limitation bullets after the abstract page. |

| REVIEWER | Adam J Olszewski  
| Brow University, USA |
| REVIEW RETURNED | 24-Jan-2017 |
GENERAL COMMENTS

In this revision, the authors addressed comments from prior reviews. The discussion is now much more readable and puts the findings in some context. Minor corrections:

- On P4 L75, references 5,6 are listed, which do not pertain to USA (contrary to the text)
- P9 L185-187 provide % sign where it should be. Harmonize all values to the same accuracy (1 decimal point).
- P13 L296 correct to “no statistically significant changes”

VERSION 2 – AUTHOR RESPONSE

Responses to Reviewer 1:

Excess mortality rate ratios (relative excess risk) were calculated in Poisson regression model for calendar periods using 1984-1993 as a reference. Method section and Strengths and Limitations section in the Abstraction page have been revised accordingly.

Responses to Reviewer 2:

- On P4 L75, references 5,6 are listed, which do not pertain to USA (contrary to the text)

The statement has been changed to “incidence continuously increased in some areas such as Europe”.

- P9 L185-187 provide % sign where it should be. Harmonize all values to the same accuracy (1 decimal point).

Revised accordingly.

- P13 L296 correct to “no statistically significant changes”

Revised accordingly.

VERSION 3 – REVIEW

REVIEWER
Sandra Eloranta
Clinical Epidemiology Unit, Dept of Medicine, Karolinska Institutet, Stockholm

REVIEW RETURNED
20-Feb-2017

GENERAL COMMENTS

The authors have updated the strength and limitation sections as well as the statistical methods section. However, the updates do not clarify the point raised in my previous response.

It is clear that calendar period of diagnosis is included in the Poisson model and what the reference category is. This is not equal to carrying out a period analysis (see for example: Brenner H, Gefeller O. Deriving more up-to-date estimates of long term patient survival. J Clin Epidemiol 1997, 50, 211–216.).

In short, what my question refers to is what the options "perbeg" and "perend" were set to in the R-program used to generate the results.

I suggest the authors remove all references (in the text as well as the references) to period analysis as it appears that the analysis that
has been done is in fact modelling of excess mortality in a classical cohort setting (unless information that makes it possible to reproduce the period analysis can be provided).

VERSION 3 – AUTHOR RESPONSE

Errors have been made when Supplemental Table 3 was prepared. Relative excess risk is actually an odds ratio from the Poisson regression model for period (treated as a categorical variable in order to generate the ORs). This table has been removed.

We ran separate 5-year relative survival period analyses for three time periods: 1984-1993, 1994-2003, 2004-2013. 1993, 2003, and 2013 are perend (p2 in the R code below) for the analyses and perbeg=perend-4 (or p2-4). I copied part of the code here:

adj.rs.male_hl <<- period(subset(rs_data,type==1 & sex==1 & dy>=p1 & dy<=p2), 5, surv.probs.males, surv.probs.females, p2-4, p2, method="edererII", agedist=cancer.pop_hl)

For time trend testing, we first ran period analysis to obtain parameters (e.g., person-years at risk) required for Poisson analysis and include period in the regression model. R code is adopted from Holleczek and Brenner (2013) and copied here:

y <- cp <- agr <- obs <- dstar <- at_risk <- NULL
for (cp_ in 1:3) {
  for (agr_ in 0:4) {
    # run conventional period analysis
    res_ <<- period(subset(nhl, agr==agr_), 5, surv.probs.males, surv.probs.females, cy_ - 4, cy_)

    obs_ <<- rowSums(res_$obs.deaths[,1])
    py_ <<- rowSums(res_$person.years[,1])
    exp_ <<- rowSums(res_$exp.deaths[,1])

    # append values
    y <<- c(y, 1:5) # follow-up year
    cp <<- c(cp, rep(cp_, 5)) # calendar time period
    agr <<- c(agr, rep(agr_, 5)) # age group
    obs <<- c(obs, obs_)
    dstar <<- c(dstar, -(py_-obs_/2)*log((py_-exp_)/py_))
    at_risk <<- c(at_risk, log(py_-obs_/2))
  }
}

## couple vectors of model variables in 'model2.df'
model2.df <<- data.frame(y=as.factor(y), cp, agr=as.factor(agr), obs, dstar, at_risk)

## fit model
model2.fit <<- glm(obs ~ y + agr + cp - 1, offset=at_risk, family=poisson(modperiod.link(model2.df$dstar)), data=model2.df)
summary(model2.fit)
## load package 'lmtest'
require(lmtest)

## carry out Wald test (H0: \( cp=0 \); H1: \( cp<>0 \))
waldtest(model2.fit, "cp", test="Chisq")
Long-term time trends in incidence, survival and mortality of lymphomas by subtype among adults in Manitoba, Canada: a population-based study using cancer registry data
Xibiao Ye, Salaheddin Mahmud, Pamela Skrabek, Lisa Lix and James B Johnston

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