Article details: 2014-0118	
Title	Trends in relative survival of patients diagnosed with hepatocellular carcinoma: A population-based cohort study
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Reviewer 1	Dr. Jeffrey Lipton
Institution	Department of Medicine, Princess Margaret Hospital, Toronto, Ont.
General comments	There are a number of issues that need to be addressed. The authors may not have the answers, but I think there should at least be a comment that will make this paper better understood for the general physician audience that reads the CMAJ. This is a very interesting and detailed manuscript that addresses changes in survival of patients with HCC over 2 decades. Although improving, outcomes are still poor and the authors suggest that improvement in prevention, diagnosis, and therapy are all important in dealing with the disease. I will deal with these sequentially. Prevention - it is my understanding and I daresay the understanding of many Canadian physicians, that the principal risk for HCC is hepatitis B. This is not really commented on in much detail. Given that this is rampant in many parts of the world, to a large part from in utero infection, how is the preventable? Is the increase in incidence noted due to increased immigration from countries where this is a more common disease, and hence the population at risk is increasing? Are there any data available on ethnicity in the data base examined? There will be data from STATSCan on the relative changes in ethnicity in Canada over the period of time examined. Does this change parallel that of the increase in HCC? What about some of the other causes of liver disease? Are there stats on hepC, alcoholism, etc. that can be commented on? Do the authors have any comments on the impact of vaccination? Diagnosis - earlier diagnosis is important. We really cannot get a sense from the paper whether HCC is being diagnosed at an earlier stage and the authors comment on this. For the lay physician, what is the basis for diagnosis? Must there be a tissue diagnosis or can it be made from imaging or an elevated AFP? A comment on how to diagnose better is appropriate here. Should this include routine hepatitis testing, AFP testing, imaging be done on at risk populations? Should certain populations be targeted for screening? What is the role for education in the at risk populations? Therapy - the authors comment of various therapies that are available, but are they available to all patients? Should patients be seen at specialized centres so that they all get access to the surgical, radiological and chemotherapeutic options that are available? Why do older people do more poorly? Are they less aggressively managed? In order to make this effort valuable to rank and file physicians, commenting on some of the issues addressed would be helpful and some general guidelines on who to screen and what to look for, could bring more patients to diagnosis at earlier ages and with earlier stage disease.
Reviewer 2	Yuri Ito
Institution	Center for Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Japan
General comments	Authors analysed trends in relative survival of hepatocellular carcinoma patients using descriptive and modelling approach. I think the manuscript needs correction for some parts. Major points 1. SMR The topic of this manuscript is focused on the trends in relative survival, then I think the part of trends in SMR is not necessary. In the abstract, the description of SMR is not correct, "Standardised mortality ratios (SMRs) were calculated using observed death from the OCR and expected deaths from Ontario life tables." If they used this approach to estimate SMRs, this is almost same as excess mortality rate ratios. Usually, in a descriptive epidemiology analysis, expected deaths for SMRs (age-standardisation using indirect method) were calculated using age-specific mortality rate from standard population (usually whole country data). In addition, to examine the trends in mortality rate, it is adequate to use age-standardised mortality rate using direct method. I recommend to remove the part of trends in SMRs (Table 1) from the manuscript. 2. Interpretation of results I would like to know much more interpretation based on the improvement in clinical treatment. Although authors described about the change in treatment in conclusion,

	but they did not show any external data about the improvement in clinical settings. Results from modelling approach should be more precise, because they analysed and found many significant differences and interactions from the models. In addition, I would like to know the reason of gender differences in relative survival. 3. Figures Not only showing the one- and five-year relative survival, but also showing the relative survival curves is much more important and useful for readers. Minor points 4. Categories of CCI In the categories of CCI, does "no hospitalization record" mean "missing"? If yes, it is better to analyse as missing data. 5. Reference In page 7, method section of regression modelling of relative survival, reference 21 appeared a lot of sentences. Probably, they do not need to add the reference in the all sentences. In page 11, first sentence of the last paragraph, authors added references 33 and 38. But the reference 33 is for life tables. Probably, they need to remove it. About the reference 40, Allemani et al published the latest results of CONCORD study in the Lancet (doi: 10.1016/S0140-6736(14)62038-9). So it is better to check the new results to interpret their results of this manuscript. 6. Table 3 and 4 I think authors do not need to show all results of modelling. To simplify, intercept and coefficients can be removed. Keeping the data of excess mortality hazard ratio, the 95% CI and p-value is enough in table 3 and 4.
Author response	<u>Reviewer #1</u> 1. See above #3 response. 2. This reviewer's comment seems to be going beyond the scope of the present research manuscript. Therefore, we did not incorporate about this in the revised manuscript. 3. We added the following texts in the "Conclusion" section on Page 13: "In view of the complexity of HCC care such as physician specialty, referral process related to place of diagnosis, and experience of the facility that affect the receipt of HCC treatment, receipt of any HCC-specific treatment is relatively low among newly diagnosed patients with any stage of HCC.50 Due to many potentially useful treatments and requirements of monitoring of liver function impairment before, during, and after therapy, a multidisciplinary approach (including hepatologists, radiologists, surgeons, pathologists, and oncologists) is essential to provide optimal outcomes for patients with HCC.51" Related to the reviewer's comment: "Why do older people do more poorly? Are they less aggressively managed?", we added below statement following this in the "Interpretation" section on page 13: "The other major aspect of this study is estimating the impact of common covariates on the relative excess mortality risk. A long-term follow-up after diagnosis and curative treatment were significantly associated with the most protective relative excess mortality risk. Being diagnosed at a later age was significantly associated with an increased relative excess mortality risk." "Poorer survival among older people may be due to the presence of higher level of comorbidity and greater number of chronic conditions that may reduce the tolerance of cancer treatments, and may be less likely referred to specialist care, which may affect treatment choices. Because of their advanced age, older people may also receive less aggressive treatment, independent of comorbidity.41,42" We agree with the editors' note about some of the reviewer's comments are interesting but they seem to be going beyond the scope of the present research manuscript. We however, responded to the reviewer's comments #1 and #2. <u>Reviewer #2:</u> Major points: 1. SMR: We agree with the reviewer's comment that the topic of this manuscript is focused on the trends in relative survival. We therefore removed the part of trends in SMRs,

	including Table 1. 2. Interpretation of results: There was a gender difference in the 1-year survival among those aged <60 years only but no differences in the survival over time in this study. A recent study by Yang et al. (Cancer 2014; 120:3707-16) using SEER database and Cox regression model showed that the sex effect on survival was more pronounced in younger (<65 years) female cohorts with HCC. However, the authors reported that the role of androgens and estrogens in the development and progression of HCC warrants further investigation. This was not reported in the manuscript. 3. Figures: We added the ten-year relative survival curves for hepatocellular carcinoma by gender in the Appendix (Figure A1). 4. Categories of CCI: According to the reviewer's comment, we added this in the "Study variables" section on page 7: "If cases did not have a hospitalization record at diagnosis date, we determined baseline comorbidity by looking back 2 years into the hospitalization data to find the most recent hospitalization record and applying the comorbidity score from that hospitalization.32 Patients were assigned as having a missing Charlson-Deyo Comorbidity Index at baseline if they had no hospitalization records at diagnosis or 2 years before diagnosis. Comorbidity was adjusted for each hospitalization after baseline." 5. Reference: We removed some references 21 in the "Regression modelling of relative survival" section on pages 8-9. We also removed reference 33 for life tables. We added recent 5-year net survival of the Canadian adults with liver cancer in the "Interpretation" section on page 12: "This study is particularly relevant when considering the 5-year relative survival of cancers in Canada. For example, a recent study by Allemani et al.40 estimated the 5-year age-standardized net survival for adults with 10 common cancers such as stomach, colon, rectum, liver, lung, breast, cervix, ovary, prostate, and leukemia. Of which, 5-year survival from colon, liver, stomach, and prostate cancers in Ontario increased between 1995-1999 and 2005-2009; the 5-year survival from liver cancer in Ontario was as follows: 1995-1999 (16.1%, 95% CI: 14.3, 18.0%); 2000-2004 (21.2%, 95% CI: 19.4, 22.9%); and 2005-2009 (24.3, 95% CI: 22.6, 26.0%). Additionally, the 5-year survival from liver cancer in Ontario was higher than other Canadian provinces in each calendar period of diagnosis.40" 6. Table 3 and 4: We removed beta coefficient, SE and p-value columns from Tables 3 and 4. Other: Several references have been changed as well.