Author’s response to reviews

Title: Association between shift work and the risk of death from biliary tract cancer in Japanese men

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Author’s response to reviews: see over
Reviewer's report

Title: Association between shift work and the risk of death from biliary tract cancer in Japanese men

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Reviewer: Mario Schootman

Reviewer's report:

Major Compulsory Revisions
The purpose of this study was to examine the association between shift work and risk of death from biliary tract cancer in Japanese men using a large cohort study of self-reported baseline data linked with death certificate data. This is an interesting study in part because of the focus on relatively rare types of cancers. Additional strengths include the cohort approach and a seemingly well characterized population. However, there are some weaknesses to the study that may affect its validity.

We appreciate the reviewer’s comments on our study. Below are our point-by-point responses to those comments.

First, at baseline 46,395 men participated in the study but only 22,224 men were included because of missing data on occupation or history of cancer at baseline. The authors should examine if the smaller group of men was similar to the 46,395 men at baseline.

We agree with the reviewer. We examined the characteristics such as sex, sex, body mass index, and cigarette smoking between 22,224 men included in the present analysis and 46,935 men at baseline. Overall there were no significant differences between the two groups. In accordance with the reviewer’s comment, we have added the following descriptions in the revised paper.

Line 72-74
We examined the characteristics such as sex, age, body mass index, and cigarette smoking between those subjects and 46,935 men at baseline. Overall there were no significant differences between the two groups.
Second, it is not clear in many instances which instruments were used to obtain the data, including their validity and reliability. For example, stress was assessed but no instrument was described. More importantly, the validity of the exposure question that assesses shift work was not included (line 75).

We thank the reviewer for raising this important point. The questionnaire used in the JACC study solicited information on demographic characteristics, medical history, lifestyle factors, and psychological traits. In addition to FFQ, no validation work has been done to address the validity and reliability of questionnaires, including questions that assess shift work. We are aware of a 2012 paper that validated a questionnaire to screen for shift work disorder. However, it was not used in the majority of cohort studies, including the Nurses’ Health Study.

We agree with the reviewer that it is important to use validated questionnaires to collect exposure information. As we wrote in the Discussion section, because the baseline exposure data were collected 20 years ago when most findings on the association between shift work and cancer had not been reported, we did not add more questions to evaluate various aspects of shift work, such as duration and chronotype.

We acknowledge this major limitation and have revised the sentences in the Discussion section.

Line 155-156

First, one major limitation is the use of simple, unvalidated questionnaire to collect exposure data on shift work in the baseline survey.

Third, the sentences on lines 54-55 are unclear. Were all participants followed up through Dec 2009 or only in 10 areas was this the case?

We apologize for the ambiguity. In the JACC Study, among 45 areas, follow-up was discontinued in 10 areas before Dec 2009 due to logistic problems. We have revised this sentence in the revised paper.

Line 54-55

We followed the study subjects until December 31, 2009 in 35 areas. Because of logistical problems, we discontinued follow-ups prior to December 31, 2009 in 10 areas.

Fourth, those who moved away from the study area were considered lost to
follow up after their moved? Line 88.

Yes. Those who moved out of the study areas were considered lost to follow up. We have revised this sentence in the revised paper.

Line 88-91

Person-years of follow-up were calculated for each cohort participant from baseline to December 31, 2009 or to the date of pancreatic cancer death, death from any cause, or the time of moving out of the study area, whichever occurred first. Subjects who died from causes other than pancreatic cancer or who moved out of the study areas were treated as censored.

Fifth, many men likely died from other causes than biliary tract cancer. Should a competing risk model have been used? If not, how could this have affected the findings?

We appreciate the reviewer’s comment. We did not perform a competing risk analysis. Compared with clinical studies, applying a competing risk approach is not common in cohort studies that address the association between lifestyle factors and one specific outcome, such as biliary tract cancer mortality in our study. However, competing risk was taken into consideration in some cohort studies in which the outcome was multiple cancers sites.

As the reviewer pointed out, it is likely that some men may die from other causes than biliary tract cancer. In this situation, using traditional Cox models without controlling for the competing risk may lead to overestimate of risk of disease. However, it is not clear whether the proportion of subjects died from other causes is equal or greater to the proportion of subjects died from biliary tract cancer.

In our study, if competing risk existed, we anticipated that the association obtained might have been weakened. Given that another reviewer did not show concern on this issue, we would use the traditional Cox hazards models without considering the competing risk.

Sixth, no additional data were collected after baseline. It could be that men who were on shift work saw declines in their health and were therefore taken off of shift work after baseline data collection. How could this have affected the findings?
The reviewer is correct. One limitation of our study is that we were not able to update exposure data after the baseline survey. As the reviewer pointed out, men who were engaged in shift work may quit during the follow-up period. Also men who were not engage in shift work at baseline may be engaged in shift work. We consider that non-differential misclassification is possible, and in this circumstance exposure-outcome association may have been weakened. More cautious interpretation is needed when only data at the baseline survey was used for analysis. We have added the following sentences in the revised paper.

Line 165-169
Second, we did not collect data on shift work after the baseline. Men who were engaged in shift work may quit during the follow-up period, and men who were not engaged in shift work at baseline may start shift work. We consider that non-differential misclassification is possible, and in this circumstance the exposure-outcome association may have been weakened.

Minor Essential Revisions
Line 87 includes pancreatic cancer death. What is the reason for this
We apologize for the mistake and have revised the sentence.
Line 89
the date of pancreatic cancer death or any other cause

Was the length of occupation as part of shift work collected?
Unfortunately we did not have data on length of occupation.

Line 174 includes the statement that stress level could have been an unknown confounder, but line 94 states the perceived stress was collected.
We apologize for the inconsistency. We have deleted the phrase ‘perceived stress’ in line 174.

Line 173-175
Third, although we adjusted for known or suspected risk factors for biliary tract cancer, it is possible that the risk estimates may have been affected by unknown confounders, such as morning preference and hormone levels.
Level of interest: An article of importance in its field.

Quality of written English: Acceptable

Statistical review: NO, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.