Peer Review File

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Reviewer A

Comment 1: Although the authors described the strength of this study as a large-scale population-based design, a previous study such as Ref. 19 has assessed second malignancies after treatments for esophageal cancer using SEER database. The
original of this study should be discussed more.

Reply 1: Thank you for the suggestion. The present study differs on several aspects with this previous study. Particularly, we stratified the analysis by histological type which was not the case in the previous study. We believe such strategy is clinically relevant because the two main histological types of esophageal cancer, i.e. squamous cell carcinoma and adenocarcinoma, differs greatly in etiology and treatment. In addition, a compete-risk model was used which could adjust for multiple risk factors and take into account the relatively high mortality in esophageal cancer patients.

Changes in the text: We have elaborated the strengths of our study as follows in the manuscript: "Although the risk of second cancer in esophageal cancer patients has been analyzed previously, the present study has the strengths including the population-based design, assessing outcome risk with multiple measures on both absolute and relative scales, separate analyses by histological type, and utilization of competing-risks regressions which might be suitable for the cohort of esophageal cancer patients with relatively high mortality" (**Line 188-193**, **2nd paragraph, Discussion**).

Comment 2: Due to the study design, data on follow-up strategies of esophageal cancer was lacking. This is a huge limitation. For example, radiological examinations like CT scan are generally performed after treatments of esophageal cancer especially in advanced stage, leading to the detection of second malignancies.

Reply 2: The population-based registries included in the analysis have follow-up process according to the rules and regulations at their institutions, which vary across registries. We agree that follow-up after esophageal cancer diagnosis may increase the chance of detection of a second cancer. Such artificially increased risk of second cancer could be related to, as mentioned by the reviewer, the tumor stage and other factors, e.g. length of follow-up. We have stratified our analysis by length of follow-up and also included tumor stage as a regressor variable in competing-risks regression. Hopefully such analysis strategies are helpful, at least partially, for interpreting potential detection of second malignancies by more frequent medical follow-up. .

Changes in the text: We have added the following statements in the revised manuscript: "Such observed increase in risk of second cancer might be, at least to some extent, due to an increased chance of detection of second cancer because of more frequent medical follow-up after esophageal cancer diagnosis. Such artificially increased risk of second cancer could be associated with the stage of esophageal cancer and other factors, e.g. length of follow-up. Therefore, the stratified analysis by length of follow-up and inclusion of tumor stage as a regressor variable in competing-risks regression would be helpful to better interpret how frequent follow-up had possibly led to detection of a second cancer" (**Line 209-217, 3rd paragraph, Discussion**).

Comment 3: Loss to follow-up in some patients can result in underestimation of second malignancies.

This should also be discussed as a limitation.

Reply 3: We agree. However, only a very small proportion (~1%) were lost to follow-up in this study, and thus, its influence on the results would be minimal.

Changes in the text: We have added the following statements in the revised manuscript: "Incomplete follow-up might have resulted in underestimated risk of second malignancies. However, only a very small proportion (~1%) were lost to follow-up in this study, and thus, its influence on our results would be minimal" **(Line 203-206, 2nd paragraph, Discussion**).

Reviewer B

Comment 1: The major risks of developmental for esophageal squamous cell carcinoma are smoking and drinking. Moreover, flashers are easy to influence these risks. The authors should examine history of smoking and drinking.

Reply 1: Thank you for the comment. We agree examining history of smoking and alcohol drinking would be helpful for understanding the observed altered risk of second cancer in esophageal cancer patients. Unfortunately, the SEER dataset based on cancer registries did not include data on smoking or alcohol drinking.

Changes in the text: We have discussed such limitation in the manuscript as follows: "due to the lack of relevant data, we were unable to analyze in detail how genetic background, lifestyle factors (e.g. smoking and alcohol drinking), physical conditions including obesity, comorbidities and oncological treatment influenced the risk of second cancer" (**Line 193-196, 2nd paragraph, Discussion**).

Comment 2: Is Years of diagnosis is associated second primary cancer types?

Reply 2: Yes, the types of second cancer differ across calendar years of esophageal cancer diagnosis. For example, we have noted a decreasing proportion of lung cancer and prostate cancer and an increasing trend in stomach cancer. However, considering the statistical uncertainty due to the limited number of cases for each cancer type (<100 for the most cancer types), we did not perform separate analyses by year of diagnosis.

Changes in the text: We have admitted such limitation in the manuscript as follows: "the number of cases remained limited for more detailed categorization of second cancer types and in some stratified analyses. Particularly, although we have noted a seemingly decreasing proportion of second lung cancer and prostate cancer and an increasing trend in stomach cancer, we were not able to evaluate in detail how second cancer types varied over calendar year of diagnosis" (**Line 197-201**, **2nd paragraph, Discussion**).

Comment 3: Is BMI associated with risk of esophageal adenocarcinoma? The authors should examine BMI.

Reply 3: Yes, obesity is a considerable risk factor for many cancer types, including esophageal adenocarcinoma. We agree examining BMI would be helpful for understanding the observed altered risk of second cancer in esophageal cancer patients. Unfortunately, the SEER dataset based on cancer registries did not include such data.

Changes in the text: We have discussed such limitation in the manuscript as follows: "due to the lack of relevant data, we were unable to analyze in detail how genetic background, lifestyle factors (e.g.

smoking and alcohol drinking), physical conditions including obesity, comorbidities and oncological treatment influenced the risk of second cancer" (**Line 193-196**, **2nd paragraph, Discussion**).