Author's response to reviews

Title: Macronutrients, vitamins and minerals intake and risk of esophageal squamous cell carcinoma: a case-control study in Iran

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Response to Reviewer

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Title: Macronutrients, Vitamins and Minerals Intake and Risk of Esophageal Squamous Cell Carcinoma in a Population at Risk for Esophageal Cancer

Version: 2

Reviewer: András Keszei

Reviewer's report:

Thank you for the opportunity to review the revised manuscript by Jessri and colleagues. My comments were answered by the authors and the manuscript has improved in my view. I have one comment regarding the analysis done in the revised work. In the fully adjusted models the authors adjust for duration of smoking measured in years, as well as smoking intensity measured in pack-years (Statistical analysis 2. paragraph). Since the calculation of pack-years already entails smoking duration, it is not practical to adjust for these two inherently correlated variables. I would suggest using either pack-year only or separate variables for duration and intensity measured by cigarettes (packs) smoked per day.

- Thank you very much for your thoughtful comment. As per suggestion of the reviewer, “duration of smoking measured in years” was removed from all fully adjusted models and we solely used “pack-year” in the analyses, which entails both the “duration and intensity” of smoking.

All data were re-analyzed accordingly and odds ratios (ORs) and 95% confidence intervals (CI) values were revised in “Table 2”, “Table 3” and “Table 4”. This has been noted in the “statistical analysis” section on page 9, line 171 and footnotes of Tables 2-4.

In addition, the manuscript text was revised to include the new corrected ORs (95% CIs) in the “abstract” section on page 2 lines 38-43, as follows:

“After adjusting for potential confounders, the risk of ESCC increased significantly in the highest tertiles of saturated fat [OR: 3.03, 95% CI: 1.05-3.41], cholesterol [OR: 2.71, 95% CI: 1.85-4.32], discretionary calorie [OR: 1.93, 95% CI: 1.15-3.94], sodium [OR: 1.74, 95% CI: 1.22-3.09] and total fat intakes [OR: 1.69, 95% CI: 1.13-2.91]. In contrast, being in the highest tertile of carbohydrate, dietary fiber and (n-3) fatty acid intake reduced the ESCC risk by 79%, 65% and 61%, respectively. The most cancer-
protective effect was observed for the combination of high folate and vitamin E intakes (OR: 0.012, 95% CI: 0.001-0.833; p<0.001).”

It was also corrected in the “results” section on page 10 lines 206-212, and page 11 lines 218-227, as follows:

“In the fully-adjusted model, those in the highest tertile of SFA intake had 3.03 times higher ESCC risk (95% CI: 1.05-3.41; p-trend=0.04), followed by those in the highest intake tertile of cholesterol (OR: 2.71, 95% CI: 1.85-4.32; p-trend<0.001), discretionary calorie (OR: 1.93, 95% CI: 1.15-3.94; p-trend=0.02) and total fat intake (OR: 1.69, 95% CI: 1.13-2.91; p-trend<0.001). On the other hand, being in the highest tertiles of carbohydrate, dietary fiber and (n-3) fatty acid reduced the risk of ESCC by 79%, 65% and 61%, respectively. In the preliminary age- and sex- adjusted analysis (original matching criteria), a positive association also emerged with an increased protein intake, which was not significant in the fully-adjusted model."

“In the fully-adjusted model, the most protective effects against ESCC risk were associated with higher intakes of folate (OR: 0.06, 95% CI: 0.01-0.83; p-trend <0.001) and vitamin E intakes (OR: 0.09, 95% CI: 0.01-0.68; p-trend<0.001), closely followed by selenium (OR: 0.13, 95% CI: 0.05-0.65; p-trend<0.001), vitamin B6 (OR: 0.21, 95% ci: 0.18-0.86, p-trend=0.01) and riboflavin intakes (OR: 0.25, 95%CI: 0.16-0.92; p-trend=0.03). Being in the highest tertile of sodium intake residual was associated with 1.74 fold increase in the ESCC risk (p<0.001). A significant inverse relationship between ESCC risk and higher intakes of α-tocopherol, thiamine and potassium observed in the base model, disappeared when other potential confounders were taken into account.
Table 4 shows the OR (95% CI) for the joint effect of vitamin E and folate intake residuals on ESCC risk. After mutual adjustment for several potential confounders, the combination of high intakes of both chemicals was associated with a strong protective effect against ESCC risk (OR: 0.012, 95% CI: 0.001-0.833; p<0.001).”

**Level of interest:** An article whose findings are important to those with closely related research interests

**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