

# Very hot tea drinking increases esophageal squamous cell carcinoma risk in a high-risk area of China: a population-based case–control study

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## Dear editor

The objective of the study titled “Very hot tea drinking increases esophageal squamous cell carcinoma risk in a high-risk area of China: a population-based case–control study” by Yang et al<sup>1</sup> was to find the effect of drinking very hot tea on the risk of esophageal squamous cell carcinoma (ESCC). We appreciate the authors for their contribution to this area with a sound methodology, design, and well conduct of the research. Though the study was appreciable, there need some clarifications in the following areas in the analysis section of the article.

The authors have mentioned that the design used is a population-based case–control study, but no justification is given about why they have included 1,355 cases and 1,962 controls in the study.<sup>2</sup> In the methodology, it is stated that the participants were selected randomly matching for age and sex, but the results shows statistically significant difference between age group and ESCC among women. This indicates that age is not properly matched among the cases and controls. As the authors have stated, age is already matched across cases and controls; hence, it is not required to adjust again by age while performing regression.<sup>3</sup>

“Never tea users” cannot be taken as a reference group to determine the effect of age at starting, duration, intensity, accumulation, temperature, and concentration of green tea on ESCC as these are applicable only for tea drinkers. Reference category is also not mentioned in any of the comparison (Table 3). While finding the risk of ESCC in association with tea use, fully adjusted OR is calculated by adjusting all factors including the factors that are not statistically significant (Tables 3–5).

The authors have mentioned that they have performed trend tests by using median within each category; however, results of the trend test are not provided in the article. While finding the joint effects of “tea drinking temperature” and “alcohol drinking intensity” on ESCC, the reference group is taken as “never users”. If the objective of the comparison is to find the joint effect of very hot tea drinking and alcohol consumption on the risk of ESCC, references cannot be “never users,” and it is better to exclude nongreen tea users from the cohort to find the “effect of temperature.”

Regression model for the net effect of green tea consumption on ESCC changes if we include explanatory variables that are not statistically significant in the simple regression model. Number of cases and control also determine the statistical significance of OR.

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## Disclosure

The authors report no conflicts of interest in this communication.

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## Authors' reply

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## Dear editor

We thank Aji Gopakumar et al for their comments in regard to our recent article on the association between very hot tea drinking and esophageal squamous cell carcinoma (ESCC).<sup>1</sup>

The details of this case-control study have been delineated in our previous articles.<sup>2,3</sup> More than 90% of cancer patients in the local area are diagnosed at the local four largest hospitals, and the missed cases can be further traced via linkage to the local Cancer Register System. During the 3-year period, we recruited about 80% of newly diagnosed esophageal cancer cases via the hospitals' endoscopy units and local Cancer Registry System. The controls were randomly selected from the general population by frequency matching to cases, thus our study design is a population-based case-control study. The inclusion criteria were those aged 40–85 years, having lived in Taixing for at least 5 years and having complete information about tea drinking history. A numeric description of the selection flow of all cases and controls might be too lengthy; however, all the details can be retrieved and referred to from the previous article.<sup>2</sup>

In terms of the details about selection of controls, a frequency-matching method was applied. Namely, all cases were categorized into multiple subgroups by sex and 5-year age groups. For each subgroup, the corresponding controls were selected from the general population via Taixing Population Registry System. Admittedly, a small difference on age distribution between ESCC cases and controls among women could be noticed. Nevertheless, the variance on average was just less than 2 years, thus the female cases and controls were relatively comparable. During the actual process of control

enrollment, some of the subjects could not participate in our study and the age ratio among women slightly deviated from the scheduled plan for various reasons, such as death prior to contact, outmigration, inability to be reached, and so on. Since in the unconditional logistic regression models, age was always included as a covariate, any residual confounding from age should have been appropriately controlled.

The original article intended to analyze the risk of tea drinking for ESCC, instead of the dose-response relationship among tea drinkers, while the subgroups of tea drinking based on different dimensions could be thought as different exposures. Therefore, when analyzing the age at starting, duration, intensity, accumulation, temperature, and concentration of tea drinking on ESCC risk, the “never tea drinking” was used as the reference group, otherwise, the effect from the lowest exposure group could not be estimated. In addition, the *P*-values from trend analysis calculated among all subjects or among tea drinkers were provided. The reference category was noted in Table 3 as “The reference group for all comparisons is never tea drinking,” and the results of trend tests were listed in each table as “*P* for trend.” For the joint effects of “tea drinking temperature” and “alcohol drinking intensity,” the reference might be optimal to remain as “never users,” since the effect of warm tea beverage could not be estimated and therefore making the reference weakened and ambiguous. The same analysis protocol could also be found in associated articles.<sup>4–6</sup>

Selection of covariates is always a controversial and difficult task in epidemiological analysis.<sup>7</sup> The aim of statistical analysis in the original article was to obtain unbiased effect estimation by controlling for potential confounders. Some factors, such as age and marital status, were not significantly different between ESCC cases and controls in our study; however, they were identified as risk factors for ESCC occurrence in previous articles.<sup>8,9</sup> Thus, these factors were added to the fully adjusted models based on prior knowledge, and whether these statistically insignificant factors added or not in the full models, the results did not change materially. Furthermore, by including these statistically insignificant factors, our analysis protocol would be more comparable with previous research studies.

## Disclosure

The authors report no conflicts of interest in this communication.

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