

# A burning question: does hot green tea drinking increase the risk of esophageal squamous cell carcinoma?

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This editorial comments on the paper “Hot green tea drinking increases esophageal squamous cell carcinoma risk in a high-risk area of China: a population-based case-control study”.<sup>8</sup>

Esophageal cancer is the eighth most common cancer worldwide, with ~456,000 incident cases diagnosed each year.<sup>1</sup> In Western countries, the incidence of disease is approximately four to six times higher in men than women; however, this disparity attenuates in eastern and less-developed countries.<sup>2</sup> Esophageal cancer ranks as the sixth most common cause of cancer-related death. The prognosis of esophageal cancer is dismal, and about 400,000 people die of the disease each year.<sup>1</sup> Five-year survival rates range from 43% for local stage to 5% for distant stage.<sup>3</sup> Primary prevention, therefore, marks a key strategy to reduce the global burden of esophageal cancer.

Esophageal cancer encompasses primarily adenocarcinoma and squamous cell carcinoma histologic subtypes. Esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC) have distinct geographic patterns and etiologies.<sup>2</sup> The incidence of EAC has risen dramatically over the past few decades, mainly among white men in Western countries where adenocarcinoma is the most common histological subtype. In contrast, the incidence rates of ESCC have declined in Western countries possibly due to public health efforts to moderate tobacco and alcohol consumption. The predominant subtype of esophageal cancer in Asian countries is ESCC. Worldwide, ESCC accounts for over 80% of all esophageal cancers.<sup>4</sup> Most esophageal cancer cases present in impoverished countries, with over half occurring in China alone.<sup>4</sup> Established risk factors for ESCC include excessive smoking and alcohol consumption.<sup>5</sup> Several studies have investigated the association of tea drinking and esophageal cancer risk, with inconclusive results.<sup>6</sup> Recent research suggests that high-temperature tea drinking may contribute to an increased risk of esophageal cancer, particularly when combined with excessive alcohol or tobacco use.<sup>7</sup>

In this issue of *Clinical Epidemiology*, Yang et al present findings from a case-control study conducted in China.<sup>8</sup> The study aimed to investigate the association of green tea drinking with the incidence of ESCC. Green tea drinking is commonplace in Asia, particularly in China. Green tea is heralded for its antioxidant, antimicrobial, and anti-inflammatory effects, yielding multiple health benefits including the prevention of diseases such as diabetes, dementia, and cancer.<sup>9-11</sup> Yang et al included 1,355 cases with ESCC and 1,962 controls frequency matched by 5-year age group and

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sex.<sup>8</sup> They conducted in-person interviews using a structured questionnaire to investigate life-long tea drinking habits. Contradictory to the aforementioned health benefits of green tea, their findings suggest increased risk of ESCC associated with ever versus never green tea drinking. This increased risk was evident in men but not in women, though there were few exposed female cases in the study. The risk was particularly elevated among men who consumed “very hot” green tea – defined as the consumption of the tea <1 minute after mixing the tea leaves with boiling water. The study findings show evidence of a dose–response association for earlier age at starting, longer duration, and higher intensity of green tea consumption. Results suggest a threshold for green tea consumption, where below 5 L/day-years showed a slightly reduced risk of esophageal cancer. However, between 5 and 25 L/day-years was associated with an approximately two-fold increased risk, with the risk leveling off at higher accumulation levels. Furthermore, the study also shows an interaction between green tea drinking and alcohol consumption, consistent with recent findings.<sup>7</sup>

Several issues warrant consideration when interpreting the findings of Yang et al’s<sup>8</sup> study. Their case ascertainment rate is impressive. They recruited about 78% of ESCC patients in their recruitment catchments area, and observed an acceptable response rate of about 70% among eligible controls. Esophageal cancer has a high case fatality rate, so rapid case ascertainment and recruitment is essential when conducting observational research on the etiology of the disease. These high response rates are commendable, particularly given concerns surrounding a general decline in participation rates in observational studies.<sup>12</sup> Yang et al<sup>8</sup> observed little difference in the age and sex distribution of responders and non-responders, reducing the possibility of selection bias. They incorporated important information on the temperature of the tea, and on potential confounders, including smoking and alcohol use. The increased risk of ESCC associated with green tea consumption in men, but not in women, is consistent with current research,<sup>7</sup> adding validity to their findings. However, it is noteworthy that here, and elsewhere, there were few exposed female cases, precluding any conclusion on the association of green tea consumption with ESCC in women.

The study harbors some limitations. The extent of exposure misclassification is an important concern in this study. Questionnaire-based case–control studies are almost inevitably prone to inaccurate recall or reverse causation. Recall bias can occur in studies where a subject undergoes an interview to ascertain information on the exposure status after a disease has occurred.<sup>13</sup> Reverse causality can occur

when individuals with disease change their exposure habits due to underlying disease-associated symptoms or heightened disease concern.<sup>13</sup> Yang et al<sup>8</sup> interviewed cases immediately after endoscopy, but before their diagnosis with ESCC. This strategy almost certainly “reduced” recall bias as the authors acknowledge, but it is unlikely to have eliminated this bias. Upper gastrointestinal endoscopy is associated with some physical discomfort, so any individual undergoing endoscopy is likely to have a strong underlying indication for such a procedure. Therefore, recall bias and reversal causality remain important limitations of this study.

The study was restricted to consumers of green tea only, as few individuals in the study population consumed other types of tea. Accordingly, the study lacks a comparison exposure group. It relied on the subjects’ own assessment of the temperature of the tea, which is also likely to have introduced misclassification. Green tea temperature was classified as “very hot”, “hot”, and “warm” based on the average time from mixing of the green tea leaves with boiling water to the time of tea drinking. This seems a robust strategy given the difficulty in accurately assessing the temperature of the tea in an observational setting (ie, in the absence of a thermometer). However, a major challenge in this study is the ability to distinguish between the impact of consuming a very hot liquid and the impact of consuming green tea on esophageal carcinogenesis. Given the length of time for tea brewing, “very hot” green tea may be a proxy for drinking very hot/boiling water. So, it seems plausible that the observed increased risk of ESCC is attributable to the liquid temperature rather than the green tea per se.

An intriguing finding in this study is the interaction of exposure to very hot green tea and high alcohol consumption. This reiterates findings from other studies;<sup>2,14</sup> one among them is a recent and substantially larger cohort study from China.<sup>7</sup> In China, consumption of strong alcoholic drinks frequently coincides with the consumption of hot tea.<sup>7</sup> Consequently, thermal injury to the esophageal lining may exacerbate any potential alcohol-induced trauma to the esophageal epithelium.<sup>14,15</sup>

The International Agency for Research on Cancer considers consumption of hot beverages as “probably carcinogenic”.<sup>16</sup> Several studies suggest an association between the consumption of very hot beverages with the risk of cancers of the oral cavity and upper gastrointestinal tract.<sup>7,17–20</sup> The findings of Yang et al’s<sup>8</sup> study endorse these data, adding weight to the current evidence. Taken together, these studies support strategies to minimize exposure to modifiable lifestyle risk factors such as hot green tea consumption, potentially aiding

the primary prevention of esophageal cancer. However, rather than spreading widespread panic among green tea drinkers, it seems wise to recommend that tea drinkers allow a little cooling time before drinking.

## Disclosure

The author reports no conflicts of interest in this work.

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