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Letter of Editor-in-Chief
High Salt Intake in Helicobacter Pylori Infected Individuals Can Significantly Increase the Risk of Gastric Cancer; a Global Analysis

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Gastric cancer is one of the top cause of cancer-related death in the world (1). Unfortunately, gastric cancer has a poor-prognosis and untreated early gastric cancer lesions will progress to advanced gastric cancer during 4-5 years (2).

Gastric cancer is a heterogeneous malignancy with multifactorial causes including socio-economic status, diet, environmental condition, genetic polymorphism as well as infectious agents particularly chronic infection by Helicobacter pylori (3). In 1994, the International Agency for Research on Cancer (IARC) announced that H. pylori is considered as class I carcinogens and etiologic cause of human gastric cancer (4).

However, a high rate of H. pylori infection in areas with a low incidence of gastric cancer remains an enigma (5). It has been suggested that H. pylori infection alone cannot cause gastric cancer without synergistic effects of lifestyle, diet, etc (6-7). On the other hand, there is evidence that dietary salt has an association with gastric adenocarcinoma (8-9). Therefore, it may that H. pylori infection and high salt intakes have synergistic effects in the development of gastric cancer. the previous studies reveal that salt cause upregulation of H. pylori cagA gene during in vitro experiments (10). We performed a comprehensive literature search in several databases including PubMed, Scopus, Embase, and Google scholar using search terms consisting "Helicobacter pylori", "Salt", "Gastric cancer", "Dietary" and "Salt intake" without limitation in time and language. The potential relevant documents were evaluated and the required data such as first author, publication year, country, total cases, the frequency of high salt intake among H. pylori-infected cases with gastric cancer or odds ratio corresponding 95% confidence intervals (95%CIs), and H. pylori diagnostic test were summarized in Table 1.

The odds ratio with 95%CIs was used to evaluate the synergistic effects between high salt intake and H. pylori infection among gastric cancer cases. Heterogeneity was assessed by I2 index and Cochrane Q-test; In addition, the presence of publication bias was measured using Begg's p-value and Egger's p-value test (18).

There were 7 case-control studies that met our criteria. These studies were conducted during 2003-2019 in Korea, Japan, United states, China, and Portugal. We evaluated data of 8,068 cases. H. pylori infection was confirmed by ELISA and UBT in these eligible studies (Table 1).

The sodium concentration was assessed by history, urinary sodium, as well as Food frequency questionnaires (FFQs) in these studies.

The frequency of gastric cancer in habitual high salt intakes with positive H. pylori infection was significantly greater than those who preference salty food with negative H. pylori infection (Chi-square: 5.33; p-value: 0.02). Our results suggested that there is a positive association between high salt intake and risk of gastric cancer in H. pylori infected-individuals (OR: 1.47; 95%CI: 1.01-2.15; p-value: 0.04; I2: 83.6; Q-value: 36.6; Begg's p-value: 0.13; Egger's p-value: 0.25) (Fig 1). Tsugane et al, 2004 were suggested that there is a significant relation between salt intake and the subsequent risk of gastric cancer in a Japanese population (19). In addition, Ge et al., 2012 provided a systematic review to show the association between Habitual dietary salt intake and risk of developing to gastric cancer using 11 retrospective single-center studies (20).

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Table 1: Baseline characteristics of included studies

First author	Year	Country	Total cases		Synergistic effects between H. pylori infection and high salt intakes (>0.3%)	H. pylori diagnostic test	Ref
Lee	2003	Korea	69	199	5.36 (95%CI: 1.14-25.1)	ELISA	11
Montani	2003	Japan	223	139	0.7 (95%CI: 0.4–1.2)	ELISA	12
Shikata	2006	Japan	2,476	NA	2.87 (95%CI: 1.14–7.24)	ELISA	13
Peleteiro	2011	Portugal	422	649	0.81 (95%CI: 0.60-1.07)	ELISA	14
Zhong	2012	China	207	410	5.34(95%CI: 2.65-8.94)	ELISA	15
Thapa	2019	USA	260	NA	1.49 (95% CI: 1.09-2.05)	ELISA	16
Shu	2019	China	829	2185	1.13 (95%CI: 1.00- 1.13)	Urease breath test	17

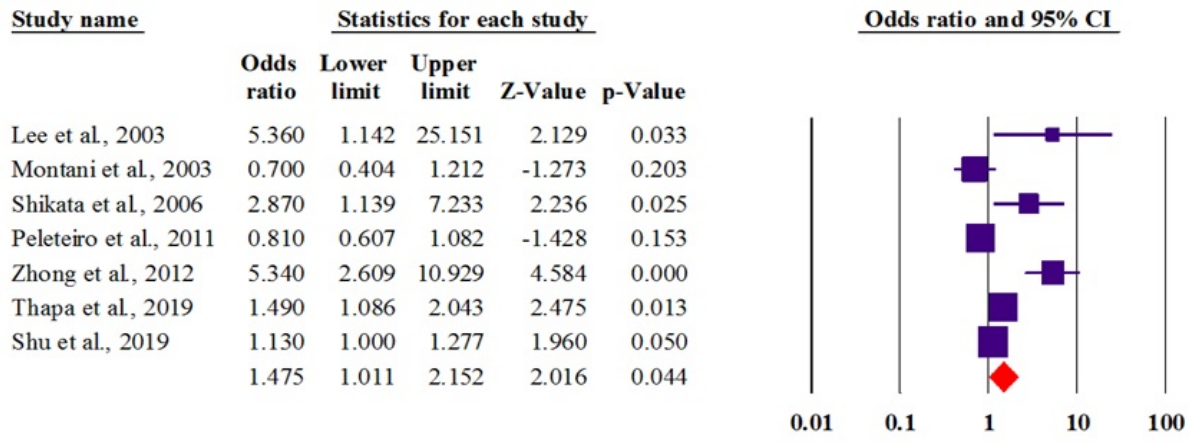

Figure 1: the forest plot of the meta-analysis on the association between higher-salt intake and H. pylori-positive infection and risk of gastric cancer using available case-control studies

Therefore, it seems that higher salt intake can be considered a risk factor for the development of gastric cancer. Otherwise, the previous studies was reveal the impact of high salt status on changes of the gene expression profile of H. pylori strain during in vitro studies (10,21). Furthermore, Fox et al., 1999 demonstrated that high salt diet feeding can induce gastric hyperplasia in C57BL/6 mice model (22). Beevers et al., 2004 found that there is a positive correlation between H. pylori infection and salt excretion in older males and females (r: 0.728 and r: 0.827, respectively) (23). In addition, Wang et al., 2008 in 67 Chinese counties were showed that there is

significant interaction between high salt consumption and H. pylori infection in the development of gastric cancer (24).

We also conducted this study and confirmed the presence of a strongly positive association between high-salt intake and risk of developing to gastric cancer in H. pylori infected individuals. Overall, we believed that concomitant H. pylori infection and favorite higher-salt intake can contribute to the development of gastric adenocarcinoma.

Conflict of interest

All authors declare that they have no conflicts of interest.

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