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Dietary Care from Premalignant Lesions to Gastric Cancer: A Multivariate Mendelian Randomization Study

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Abstract. Due to observational studies on the role of type of food in have been inconsistent, the objective of this study was to apply the MR framework to evaluate the causal link between dietary intake and gastric ulcer to provide suggestions for preventive intervention strategies. Mendelian randomization test was conducted to assess the impact of 26 types of dietary habits and macronutrient intake on of GC and precancerous lesions. Genetically predicted alcoholic drinks per week were strongly connected with. Potential evidence , fat, and cooked vegetable intake might increase tumors. Salad/raw vegetable intake may decrease . Dietary composition and habits are causally related to GC and precancerous lesions. The biological heterogeneity of food processed in different ways and type of food may be a risk factor for GC. Intensive attention should be paid to lifestyle and diet management.

Keywords: Gastric ulcer, Gastric cancer, Mendelian randomization, Dietary care, Chronic atrophic gastritis

1. Introduction

Stomach cancer continues to be the fifth most prevalent cancer diagnosed worldwide and the third major cause of cancer-related death [1]. Although the effectiveness of treatments for gastric carcinoma has increased over the preceding ten years, the survival rate of patients with gastric carcinoma remains unfavorable [2]. Therefore, risk stratification and primary and secondary prevention of stomach cancer have attracted worldwide attention [3-5]. According to Correa's model, chronic atrophic gastritis (CAG) is one of the main premalignant lesions in gastric cancer (GC) [6]. The risk of GC in patients with peptic ulcer disease can be decreased by early Helicobacter pylori eradication [7], which indicates that peptic ulcer, H. pylori, and GC are closely associated with each other. To reduce the incidence of GC, indications for H. pylori treatment including gastroduodenal ulcer have been designated in Japan [8].

Over the past H. pylori is the most important cause [9]. A cohort study in Japan demonstrated that atrophic gastritis increased the risk of GC, but dietary adjustments hinder the transition from

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atrophic gastritis to GC, irrespective of precancerous lesions [10]. To develop recommendations for GC prevention, it is important to clarify the causal association between diet and stomach disease. Nevertheless, there are scarce prospective studies examining the link between dietary lifestyle and GC risk. Thus, direct evidence of the causal impact of dietary factors on gastric ulcers, CAG, and malignant gastric tumors remains insufficient.

Considering the uncertainty pertaining to the causal link between dietary intake and gastric ulcers, CAG, and gastric malignant tumors, Our objective was to apply the MR framework to assessing the causal link between dietary intake and gastric ulcers, chronic atrophic gastritis, and gastric malignant tumors. This study underscores the necessity of dietary management from gastric premalignant lesions to GC, and provides constructive suggestions in clinical nursing education for preventive intervention strategies.

2. Materials and methods

2.1. Exposure: intake of macronutrient (dietary composition) data and dietary habits

GWAS summary statistics of four macronutrient dietary compositions (carbohydrates, sugar, protein, and fat) were conducted by the Social Science Genetic Association. This study identified six fatintake-related single nucleotide polymorphisms (SNPs), seven protein intake-related SNPs, nine sugar-related SNPs, and 13 carbohydrate intake-related SNPs ($P<5\times10^{-8}$) within the phenotype. The details of this study can be found in Meddens et al [11].

GWAS data for dietary component intake phenotypes were acquired either directly or indirectly from the UK Biobank (UKB) by the Integrative Epidemiology Unit (IEU) open GWAS Project. Diet-related component intake phenotypes used in this study included the following: cereal, meat (poultry, beef, fish, pork, processed meat, and lamb/mutton intake), vegetable (salad/raw vegetable and cooked vegetable intake), fresh fruit, and beverage (alcoholic drinks, tea, hot drink temperature, coffee, water, fizzy drink, and milk intake) intake, food intake (crisp, cheese, starchy food, dark chocolate, and ice cream intake), and type of diet (salt added to food and low-calorie diet).

2.2. Outcomes in Genome-Wide Association Study (GWAS): gastric ulcers, chronic atrophic gastritis, and gastric malignant tumors

GWAS summary statistics for gastric ulcers, CAG, and gastric malignant tumors were retrieved from FinnGen Consortium R9 release data, which encompassed 377,277 participants [12, 13]. Summary-level genetic data on gastric ulcers, CAG, malignant neoplasm of the stomach, and adenocarcinoma of the stomach were used in this study.

2.3. Study design

Using GWAS summary statistics, this study employed MR analysis [14, 15] to investigate the causal impacts of macronutrient consumption and dietary behaviors on gastric ulcers, CAG, and malignant neoplasms of the stomach. For the primary MR results, multiple testing significance was detected using n, with n representing the quantity of exposure factors). We also considered the nominal significance level for the MR results to be $P < 0.05$.

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2.4. Mendelian randomization analyses

Four MR analyses were employed to evaluate the causal impacts of macronutrient consumption and dietary behaviors on gastric ulcers, CAG, and gastric malignant neoplasms. The primary analysis utilized standard inverse variance-weighted (IVW) estimates. Additionally, the weighted median (WM), MR-Egger regression, and MR-PRESSO methods were implemented as supplementary analyses to IVW

2.5. Sensitivity analyses

When genetic variants linked to the exposure (dietary habits) directly influence the outcome (malignant tumors of the stomach) through several pathways rather than the postulated exposure, it lead Steiger filtering was utilized to investigate whether the observed association harbored bias stemming from reverse causality

3. Results

3.1. Mendelian randomization estimates

3.1.1. Gastric ulcers and chronic atrophic gastritis

Within the range of dietary behavior phenotypes examined, findings from the IVW analysis revealed that the weekly intake of alcoholic beverages (OR=1.95; 95% CI, 1.33–2.86; P=0.00059) were associated with an elevated risk of CAG (Figure 1a–b). Consistent causal effect estimates pertaining to CAG were additionally derived from MR-PRESSO regression analyses (OR=1.95; 95% CI, 1.47–2.59; P=0.000082), whereas WM analysis (OR=2.34; 95% CI, 1.36–4.03; P=0.0022) presented a nominally significant result. Moreover, we found a potential causal association between salad/raw vegetable intake and CAG (OR=0.41; 95% CI, 0.19–0.89; P=0.025), which did not pass the Bonferroni test(Figure 1c–d).

Although a nominally significant causal association between poultry intake and CAG was obtained from IVW (OR=4.78; 95% CI, 1.33–17.26; P=0.017) and WM (OR=7.52; 95% CI, 1.77–31.91; P=0.0062), the MR-Egger analysis result (OR=3.75×10–12; 95% CI, 4.29×10–27–3278; P=0.19) showed the opposite and nonsignificant direction. After a strict instrument P value threshold was applied and recalculated (P<2×10−8), MR-Egger analysis results maintained an opposite and nonsignificant direction (OR=4.38×10–06; 95% CI, 1.75×10–26–1.09×10+15; P=0.70). The risk of gastric ulcer increased with beef intake (OR=2.89; 95% CI, 1.05–7.91; P=0.039) and salt added to food (OR=1.55; 95% CI, 1.11–2.14; P=0.0092). Moreover, lamb/mutton intake (OR=2.12; 95% CI, 1.13–3.99; P=0.019) increased the risk of CAG. Nevertheless, MR approaches exhibited an opposing direction, indicating that the MR estimates were violated.

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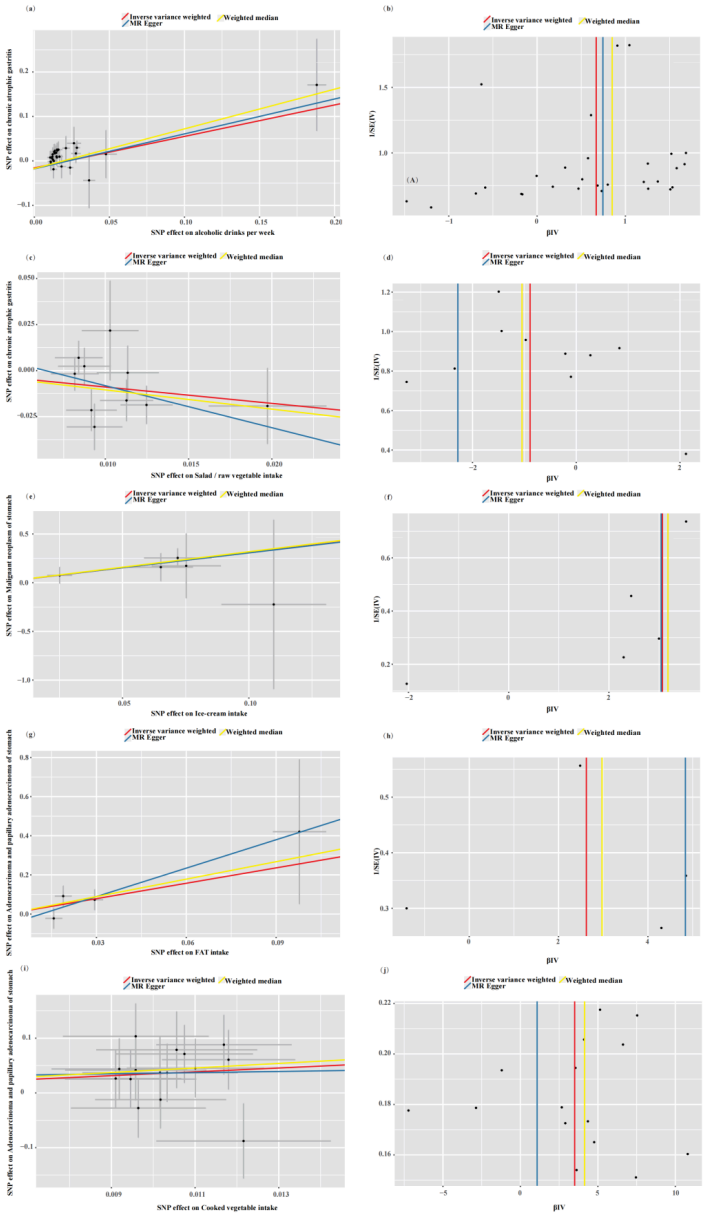

Figure 1. Scatterplots and funnel plots from genetically predicted exposure on outcome. a, b Genetically predicted alcoholic drinks per week on chronic atrophic gastritis. c, d Genetically predicted salad/raw vegetable intake on chronic atrophic gastritis. e, f Genetically predicted ice cream intake on malignant neoplasm of the stomach. g, h Genetically predicted fat intake on adenocarcinoma of the stomach. i, j Genetically predicted cooked vegetable intake on adenocarcinoma of the stomach

3.1.2. Gastric cancer (malignant neoplasm- and adenocarcinoma of the stomach)

Among the IVs with $P<5\times10^{-7}$, a causal association was identified between ice cream consumption and both malignant neoplasms (OR=21.49; 95% CI, 2.749–168.50; P=0.0035) (Figure 1e–f) and gastric adenocarcinomas (OR=26.38; 95% CI, 1.10–634.71; P=0.044). Furthermore, our findings revealed potential causal links between dietary behaviors and GC.

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In the IVW model (Figure 1g–j), genetically predicted fat consumption (OR=13.75; 95% CI, 1.09–173.28; P=0.042) and intake of cooked vegetables (OR=33.19; 95% CI, 2.12–519.91; P=0.013) were significantly linked to an elevated risk of gastric adenocarcinoma. Consistent causal effect estimates for this outcome were also yielded by the weighted median (WM) models.

3.2. Sensitivity analyses

To verify the stability and reliability of the aforementioned findings, a series of sensitivity analyses were performed (Table 1). All P-values from the MR-Egger intercept tests were >0.05, and the Cochrane Q statistics revealed no significant heterogeneity (P>0.05), which confirms that the aforementioned findings were not affected by pleiotropic bias. The funnel plots were symmetrical (Figure 1b, d, f, h, j). However, LOO analysis showed that the causal association between ice cream intake and adenocarcinoma of the stomach was driven by rs145248784, indicating that the MR estimates were violated. Moreover, Steiger tests were conducted to evaluate reverse causation effects. No evidence of reverse causation was identified in relation to the aforementioned MR results (P<0.05), when using the Steiger approach.

Table 1. Sensitivity analyses regarding the causal links between macronutrient consumption, dietary behaviors, and the risk of developing gastric ulcers, chronic atrophic gastritis, and gastric cancer

Outcome	Exposure	Cochran Q test		MR-Egger		MR-PRESSO Global Test P value
		Q value	P	Intercept	P	
Chronic atrophic gastritis	Alcoholic drinks per week	15.56	0.97	–0.001	0.85	0.97
	Salad/raw vegetable	10.96	0.28	0.01	0.45	0.32
	Poultry	8.12	0.23	0.30	0.17	0.28
Malignant neoplasm of the stomach	Ice cream	0.65	0.96	0.001	0.99	0.94
	Fat	2.30	0.51	–0.06	0.57	0.63
Adenocarcinoma of the stomach	Cooked vegetable	8.88	0.84	0.03	0.88	0.85
	Ice cream	5.79	0.22	–0.04	0.89	0.37

4. Discussion

Owing to the high incidence and poor survival rate of stomach cancer, risk stratification has attracted worldwide attention [1, 3-5]. Gastric ulcers and CAG caused by H. pylori infections are associated with an increased risk of GC [6, 7]. CAG is one of the main premalignant lesions of GC [6]. Additionally, other acquired risk factors, including dietary habits, have a significant effect on GC, although chronic infection with H. pylori stands as the paramount etiological factor underlying GC [9]. Prior research has revealed that persistent alcohol misuse renders patients susceptible to atrophic gastritis [16]—a finding that aligns with our results. A intervention trial conducted in

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Chinese communities demonstrated that smoking and drinking behaviors constitute the most critical factors contributing to the failure of H. pylori eradication in male patients [17]. Therefore, alcohol control may decrease the risk of CAG and GC by reducing atrophic inflammation of the gastric mucosa and improving H. pylori eradication rate.

A small case-control study including patients with advanced CAG reported that vegetable intake was a protective factor associated with the development of CAG and GC [18]. However, our results are not consistent with these findings. Our results suggest that salad/raw vegetable intake may decrease the risk of CAG. Conversely, s may increase the rate of stomachunder high heat and seasoned. During s, such as potato and cereal products, Acrylamide is generated through the Maillard reaction [19, 20]. This agent is identified as neurotoxic and a potential carcinogen [21] Additionally, recent research has shown that cooking oils subjected to repeated high-temperature heating can generate multiple substances, some of which have been reported as carcinogenic [22], such as benzo(a)pyrene [23]. Moreover, recent studies have indicated that cooking may reduce the nutrient content of vegetables, including vitamins [24], phenols, and glucosinolates [25]. The above studies implicated the biological heterogeneity behind food processed in different ways and indicated the importance of different dietary modes.

Taken together, our findings suggest that dietary composition and habits are causally associated with GC and premalignant lesions of GC and that primary and secondary prevention of stomach cancer deserve particular attention. Therefore, residents should pay H. pylori. Moreover, residents should pay attention to dietary management, such as avoiding alcohol consuming fresh vegetables. In addition, in the process of clinical nursing education, nursing staff should strengthen the propaganda and education on patients' diet management.

Certain limitations are inherent to the present study. Initially, the research was restricted to participants of European descent, precluding the immediate extension of its findings to ethnic groups characterized by distinct cultural contexts and lifestyle behaviors. Moreover, as MR approaches derive causal inferences through the exploitation of random genetic variant distribution, complete differentiation between mediating processes and pleiotropic effects remains a challenge. A substantial proportion of genomic variants are liable to impact multiple phenotypic characteristics. Given the inherent constraints of the current data, follow-up investigations are necessary to verify causal relationships and unravel underlying mechanisms—two prerequisites for the development of evidence-based clinical guidelines.

5. Conclusion

Using genetic summary data, our investigation reinforces the evidentiary basis for dietary composition and habits are causally associated with GC and premalignant lesions of GC. The biological heterogeneity of food processed in different ways and type of food may be a risk factor for gastric cancer. Nevertheless, supplementary studies are imperative to elucidate these associative patterns and decipher the underlying molecular mechanisms, thereby refining the scientific understanding of diet-related GC pathogenesis. Given the high incidence and poor survival rates of GC, intensive attention should be paid to lifestyle and diet management. In the process of clinical nursing education, patients were advised to eat more raw vegetables and avoid bad diets such as drinking.

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