Role of Antioxidants in The Prevention and Treatment of Gastric Cancer – A Short Review

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Abstract

Gastric cancer incidence and mortality are highly variable by region and highly dependent on diet and Helicobacter pylori infection. There are a number of protective and risk factors for gastric cancer in diet. Consumption of total fruit and white vegetables, but not total vegetables, was inversely associated with gastric cancer risk. The intake of antioxidant equivalents was inversely associated with the risk of both cardia and distal gastric cancer. Antioxidants do not aid in the prevention of gastrointestinal cancers in the general population; however, they may act as chemo-preventive agents for stomach and esophageal cancers, especially in high-risk populations. Tocopherols were associated with higher risk of GCC, whereas dietary intake of fruits, vitamin C, tocopherols, and lycopene seemed protective for GNCC.

Keywords: gastric cancer, antioxidants, fruits & vegetables, vitamins, dietary fibre

1 INTRODUCTION

Gastric cancer remains one of the most common and deadly cancers worldwide, especially among older males. Based on GLOBOCAN 2018 data, stomach cancer is the 5th most common neoplasm and the 3rd most deadly cancer, with an estimated 783,000 deaths in 2018. Gastric cancer incidence and mortality are highly variable by region and highly dependent on diet and Helicobacter pylori infection. While strides in preventing and treating H. pylori infection have decreased the overall incidence of gastric cancer, they have also contributed to an increase in the incidence of cardia gastric cancer, a rare subtype of the neoplasm that has grown 7-fold in the past decades. A better understanding of the etiology and risk factors of the disease can help reach a consensus in approaching H. pylori infection. Dietary modification, smoking cessation, and exercise hold

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promise in preventing gastric cancer, while genetic testing is enabling earlier diagnosis and thus greater survival (1).

Most of the reported studies on gastric cancer from India are case report or case series and few are case-control studies. Indian studies on this topic are limited and have observed *H. pylori* infection, salted tea, pickled food, rice intake, spicy food, soda (additive of food), tobacco and alcohol as risk factors for gastric cancer. More research is required to understand the etiology, develop suitable screening test, to demarcate high-risk population and to develop and evaluate the effect of primary prevention programs (2).

2 | THE ASSOCIATIONS BETWEEN DIETARY FACTORS AND GASTRIC CANCER RISK

The associations between dietary factors and gastric cancer risk have been analyzed by many studies, but with inconclusive results. (3) conducted a meta-analysis of prospective studies to systematically investigate the associations. Relevant studies were identified through searching Medline, Embase, and Web of Science up to June 30, 2015. They included prospective cohort studies of intake of dietary factors with risk estimates and 95% confidence intervals for gastric cancer. Seventy-six prospective cohort studies were eligible and included in the analysis. They ascertained 32,758 gastric cancer cases out of 6,316,385 participants in relation to intake of 67 dietary factors, covering a wide range of vegetables, fruit, meat, fish, salt, alcohol, tea, coffee, and nutrients, during 3.3 to 30 years of follow-up. Evidence from this study indicated that consumption of total fruit and white vegetables, but not total vegetables, was inversely associated with gastric cancer risk. Both fruit and white vegetables are rich sources of vitamin C, which showed significant protective effect against gastric cancer by our analysis too. Furthermore, they found concordant positive associations between high-salt foods and gastric cancer risk. In addition, a strong effect of alcohol consumption, particularly beer and liquor but not wine, on gastric cancer risk was observed compared with non-drinkers. Dose-response analysis indicated that risk of gastric cancer was increased by 12% per 5 g/day increment of dietary salt intake or 5% per 10 g/day increment of alcohol consumption, and that a 100 g/day increment of fruit consumption was inversely associated with 5% reduction of risk. (4) Their study provides comprehensive and strong evidence that there are a number of protective and risk factors for gastric cancer in diet. These findings may have significant public health implications with regard to prevention of gastric cancer and provide insights into future cohort studies and the design of related clinical trials.

Dietary antioxidants, with additive and synergistic effects, can mediate the observed inverse association between plant food intake and risk of gastric cancer. (5) investigated whether the total dietary antioxidant potential of fruit and vegetables is an appropriate means of estimating the antioxidant impact on gastric cancer risk in a large population-based study. Data were collected through face-to-face interviews with 505 newly diagnosed gastric adenocarcinoma patients and 1116 control subjects to assess dietary habits 20 years before interview. The total radical-trapping antioxidant potential (TRAP) of different plant foods was used to convert food frequency intake into antioxidant potential. Gastric cancer risk in groups exposed to higher levels of oxidative stress (smoking and *Helicobacter pylori* infection) was also examined. They report that the intake of antioxidant equivalents was inversely associated with the risk of both cardia and distal gastric cancer (odds ratio [OR], 0.65; 95% confidence interval [CI], 0.48-0.89 for the highest quartile of TRAP). Controlling for smoking, the inverse relationship between TRAP values displayed a clearer dose-response pattern. Never-smokers with the highest antioxidant intake had the lowest risk of cancer, 0.44 (95% CI, 0.27-0.71). Among *H. pylori*-infected subjects, the ORs varied between 0.66 and 0.41 for increasing levels of antioxidant potential. Their results suggest that dietary intake of antioxidants measured as total antioxidant potential is inversely associated with risk of both cardia and distal cancer. The innovative approach used in this study provides a new tool for investigating the relationship between dietary antioxidants and...
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oxidative stress-related carcinogenesis.

3 | BENEFITS OF ANTIOXIDANTS FROM FRUITS AND VEGETABLES

Consumption of fruit and vegetables has been inversely related to gastric cancer. Two studies found that dietary antioxidant capacity has some role in explaining this association. We investigated the overall antioxidant effect from diet on gastric cancer using three measures of non-enzymatic antioxidant capacity (NEAC). Praud, et al., (2015) used data from an Italian case-control study including 230 patients with incident, histologically confirmed gastric cancer, and 547 frequency matched controls admitted to the same hospitals for acute non-neoplastic diseases. A reproducible and valid food frequency questionnaire was used to assess subjects’ usual diet. NEAC was measured using Italian food composition tables in terms of Trolox equivalent antioxidant capacity (TEAC), Ferric reducing-antioxidant power (FRAP) and Total radical-trapping antioxidant parameter (TRAP). They estimated the odds ratios (OR) of gastric cancer and the corresponding 95% confidence intervals (CI) using conditional logistic regression models including terms for recognized gastric cancer risk factors and total energy intake. NEAC was inversely related with gastric cancer risk with ORs for the highest versus the lowest quintile of 0.54 (95%CI, 0.33-0.88) for TEAC, 0.67 (95%CI, 0.42-1.07) for FRAP and 0.57 (95%CI, 0.36-0.90) for TRAP. They concluded that a diet rich in antioxidant capacity reduced gastric cancer risk, suggesting a high consumption of fruit and vegetables and a moderate consumption of wine and whole cereals.

In-vitro and in-vivo studies in animals continue to support the hypothesis that antioxidants reduce the risk of gastrointestinal cancers. Results in human populations are not as supportive. Antioxidant nutrients and fruits and vegetables do not seem to confer protection against colorectal cancer, and certain antioxidants were found to increase the risk of distal colon cancer. Individual antioxidants also do not help prevent pancreatic cancer. Total antioxidant intake and plant-based foods seem promising for stomach cancer prevention, while vitamin C lowers the risk of esophageal cancer. Preventive effects for stomach and esophageal cancers were often limited to or stronger in smokers. Evidence is scarce regarding antioxidants and liver cancer. Antioxidants do not aid in the prevention of gastrointestinal cancers in the general population; however, they may act as chemo-preventive agents for stomach and esophageal cancers, especially in high-risk populations (6).

A high intake of dietary antioxidant compounds was hypothesized to be an appropriate strategy to reduce gastric cancer (GC) development by Serafini, et al., (2012). They investigated the effect of dietary total antioxidant capacity (TAC) in relation to GC in the European Prospective Investigation into Cancer (EPIC) study including 23 centers in 10 European countries. A total of 521,457 subjects (153,447 men) aged mostly 35–70 years old, were recruited largely between 1992 and 1998. Ferric reducing antioxidant potential (FRAP) and total radical-trapping antioxidant parameter (TRAP), measuring reducing and chain-breaking antioxidant capacity were used to measure dietary TAC from plant foods. Dietary antioxidant intake is associated with a reduction in the risk of GC for both FRAP (adjusted HR 0.66; 95%CI (0.46–0.95) and TRAP (adjusted HR 0.61; 95%CI (0.43–0.87) (highest vs. lowest quintile). The association was observed for both cardia and noncardia cancers. A clear effect was observed in smokers with a significant reduction in GC risk for the fifth quintile of intake for both assays (highest vs. lowest quintile: adjusted HR 0.41; 95%CI (0.22–0.76) p for trend <0.001 for FRAP; adjusted HR 0.52; 95%CI (0.28–0.97) p for trend <0.001 for TRAP) but not in nonsmokers. In former smokers, the association with FRAP intake was statistically significant (highest vs. lowest quintile: adjusted HR 0.41; 95%CI (0.22–0.76) p for trend <0.001 for FRAP; adjusted HR 0.52; 95%CI (0.28–0.97) p for trend <0.001 for TRAP) but not in nonsmokers. In former smokers, the association with TRAP intake was statistically significant (highest vs. lowest quintile: adjusted HR 0.41; 95%CI (0.21–0.75) p < 0.05); no association was observed for TRAP. Dietary antioxidant intake from different sources of plant foods is associated with a reduction in the risk of GC (7).

4 | BENEFITS OF VITAMINS

The association between vitamin intake and gastric cancer (GC) has been widely debated due to the
relatively weak evidence. In this study (8), a meta-analysis of prospective and well designed observational studies was performed to explore this association. The RR of gastric cancer in the group with the highest vitamin intake was compared to that of the lowest intake group. Total vitamin intake was 0.78 (95% CI, 0.7120.83). In 9 studies that individuals were given doses at least 4 times above the tolerable upper intake (UL) vitamins, the RR was 1.20 (95% CI, 0.9921.44). However, in 17 studies that individuals received doses below the UL, the RR was 0.76 (95% CI, 0.6820.86). Dose-response analysis was conducted on different increments in different types of vitamins (vitamin A: 1.5 mg/day, vitamin C: 100 mg/day, vitamin E: 10 mg/day) intake with a significant reduction in the risk of gastric cancer, respectively, 29% in vitamin A, 26% in vitamin C, and 24% in vitamin E. This meta-analysis clearly demonstrated that low doses of vitamins can significantly reduce the risk of GC, especially vitamin A, vitamin C and vitamin E (8).

For Gastric Cardia Cancer (GCC), high dietary intake of retinol was protective [hazard ratio (HR), 0.46; 95% confidence interval (95% CI), 0.27-0.78], but high intake of α-tocopherol (HR, 2.06; 95% CI, 1.20-3.54) and γ-tocopherol (HR, 1.94; 95% CI, 1.13-3.34) increased risk. For Gastric Non-Cardia Cancer (GNCC), higher intakes of fruits (HR, 0.51; 95% CI, 0.37-0.71), vitamin C (HR, 0.60; 95% CI, 0.41-0.86), α-tocopherol (HR, 0.78; 95% CI, 0.55-1.10), γ-tocopherol (HR, 0.69; 95% CI, 0.49-0.96), and lycopene (HR, 0.67; 95% CI, 0.47-0.95) were protective. These results suggest a difference in the effect of some of these exposures on GCC and GNCC. Tocopherols were associated with higher risk of GCC, whereas dietary intake of fruits, vitamin C, tocopherols, and lycopene seemed protective for GNCC (9).

5 | CONCLUSION

Gastric cancers is one of the common cancers in India, studies are required to understand the etiology and prevention of gastric cancer. Consumption of fruits and vegetables in the daily diet may prove to be beneficial in the prevention and treatment of gastric cancers. Dietary antioxidants, with additive and synergistic effects, can mediate the observed inverse association between plant food intake and risk of gastric cancer. Dietary antioxidant intake from different sources of plant foods is associated with a reduction in the risk of GC. Higher dietary intake of fruits, vitamin C, tocopherols, and lycopene seemed protective for GNCC. There is a positive association between the intake of high-salt foods and gastric cancer risk. More research is required to understand the etiology, develop suitable screening test, to demarcate high-risk population and to develop and evaluate the effect of primary prevention programs.

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