Patterns of Nutrient Intake in Relation to Gastric Cancer: A Case-Control Study

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INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer globally [1]. Based on the global cancer observatory, about 77,000 (8%) of cancer deaths were due to GC in 2020 [2]. GC is the most common cause of cancer death in Iran [3], where 14,656 GC occurred, and 12,994 patients died in 2020. *Helicobacter pylori* infection, tobacco use, alcohol consumption, obesity, and dietary factors are the main risk factors of GC [1, 4-8]. A systematic review showed a two-fold difference in the risk of GC between healthy (i.e., rich in fruits and vegetables) and unhealthy (i.e., full of starchy foods, meat, and fats) diets [9]. The association of nutrient intake with GC has been investigated in previous studies [10, 11]. Numerous studies have examined the effect of single nutrients on GC risk. An Italian case-control study reported four nutrient patterns, including animal products, vitamins and fiber, vegetable unsaturated fatty acids, and starch-rich patterns. There was a positive association between gastric cancer risk and the "animal products" and the "starch-rich" patterns. The "vitamins and fiber" pattern was inversely associated with GC and there was no significant association between GC and the "vegetable unsaturated fatty acids" pattern [12]. Antioxidant vitamins like vitamin C and E can scavenge free radicals, inhibit nitrosamine formation, and eradication of *H. pylori* [13-15]. Willett and Buzzard suggested focusing on whole nutrients as an exposure rather than single nutrients while studying the associations between dietary factors and cancer risk. This approach provides several advantages, including detecting cumulative effects that could be sufficiently large to be detectable [16]. Besides, combining nutrients into "factors" allows researchers to evaluate interactions and synergic effects of different nutrients, which is not detectable by traditional analysis [17].

Existing evidence on the association between nutrient patterns and gastric cancer has been published mainly from Western and high-income countries [10, 12, 18]. Data from the low- and middle-income countries are limited [19]. We aimed to study the association of major nutrient patterns and the risk of gastric cancer in Iran.

METHODS

Study design and sample: This study is a hospital-based case-control study conducted at the Cancer Institute of Iran between 2010 and 2012.

Cases were 178 histopathologically confirmed gastric cancer patients admitted to the Cancer Institute of Iran, referring from all parts of Iran. Patients were incidence cases who were diagnosed as GC less than one year prior to the recruitment without previous diagnosis of any cancer. Controls were 271 healthy caregivers or visitors of patients who were admitted to the same hospitals. We did not recruit relatives and friends of the cases and individuals who were visiting GC patients. We also excluded if participants had a cancer diagnosis previously and if they did not want to participate to this study. We recruited healthy controls as dietary intakes of patients are usually changed because of different disease conditions. Controls were frequency-matched with cases by residential places, age (5-year categories), and sex.

Ethical consideration

All participants signed written informed consent, and the Ethical Committee of Tehran University of Medical Sciences (Code: 17198) approved this study.

Risk factors

Trained interviewers collected sociodemographic, general information, and risk factors through a structured questionnaire via a face-to-face interview. We collected self-reported smoking status and classified it into ever and never-smoking. Venous blood (10 cc) was collected from all participants to study *H. pylori* infection status, based on the *H. pylori* (antibody in serum samples).

Dietary Assessment

Trained nutritionists interviewed both cases and controls and collected dietary information by a Persian version of the Diet History Questionnaire (Persian-DHQ), validated before by our research group. The detail about the process and validation of the Persian-DHQ has been published elsewhere [20]. Briefly, Persian-DHQ includes 146 questions related to the consumption of foods and Iranian mixed dishes. GC patients were asked to recall their intake one year before the diagnosis. DHQ contained questions about dietary supplement consumption to dismiss people who take supplements. However, it was not common in our study population and no one had excluded for this reason.

Energy and nutrient intakes were extracted using a Food Composition Table. As the Iranian Food Composition Table includes only raw foods and limited nutrients (16), we used McCance and Widdowson's Food Composition Table [21], and was supplemented with the Iranian ones for some special Iranian foods [22].

Anthropometric Assessment:

As gastric cancer affects the weight of patients, we could not rely on the measurement of the weight during the interview. Therefore, we asked the GC patients report their weight and height before the diagnosis. To be consistent, we also used self-reported measures of weight and height from the controls. The Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Statistical Analysis:

Energy-adjusted nutrient intakes were calculated as the residuals from the regression model, with absolute nutrient intake as the dependent variable and total energy intake as the independent variable [23]. Factor analysis was run to explain the total variation in intake of 26 nutrients. It should be noted that vitamin D was not considered in factor analysis due to low levels of this vitamin in foods in Iran [24]**.** In order to detect uncorrelated factors, factor scores were rotated by using varimax rotation. We used Eigen values of >1.5 in conjunction with considering scree plot to extract major patterns of nutrients. We used Kaisere Meyere Olkin (KMO) test to examine if the distribution of the different nutrients allows the use of principal components. By summing intakes of nutrients weighted by their factor loadings, the factor score for each pattern was calculated and each patient received a factor score for each pattern. Then scores were used to assess the relation of each nutrient pattern with the risk of gastric cancer.

Participants were categorized into tertiles based on nutrient patterns scores. General characteristics and dietary intakes (energy-adjusted) were examined across tertiles of nutrient patterns scores using one-way ANOVA, ANCOVA, and chi-square test. Odd Ratios (OR) and 95% confidence intervals (CI) of GC according to tertiles of nutrient pattern scores were reported using unconditional multiple logistic regression models. We considered two models, where we adjusted for age and sex in model A and adjusted for age, sex, BMI, education, smoking, and *H. pylori* in model B. To compute the overall trend of ORs across increasing tertiles of nutrient patterns scores, we used the tertiles of each pattern as an ordinal variable in the logistic regression models.

We used Statistical Package for Social Sciences Software (SPSS) version 22 (SPSS Inc., Chicago, IL, USA) for statistical analyses. We considered a two-sided $P<0.05$ as a statistically significant result.

Results

Study participants were 178 GC patients and 271 controls. Patients with gastric cancer were older (60.8 vs. 53.2 y) and less likely to be males (63.8 vs. 74.2 %) than controls. Table 1 shows the distribution of sociodemographic variables among cases and controls. In Supplementary Table 1 selected risk factors among men (*n* =305) and women (*n* =144) are shown. Age, education, smoking, and *H pylori* status were significantly different between groups. Compared with the controls, cases were significantly older, less educated and more likely to be smokers. In the cases and controls, 62.4 (*n* =111) and 26.6% (*n* =72) were illiterate, respectively.

Intake of carbohydrate, cholesterol, and niacin was greater in cases than controls. Table 2 shows the characteristics of participants according to tertiles of nutrient patterns scores. For the first and second nutrient patterns, individuals in the first tertile significantly were less infected by *H. pylori*.

We identified three nutrient patterns through the use of factor analysis. The KMO value was 0.78, indicating good sampling adequacy. Overall these nutrient patterns explained 70% of the variance. Table 3 shows factor loading for each pattern. Factor 1 explained 35.8% of the total variance and had high loadings for pantothenic acid (vitamin B5), riboflavin, zinc, animal protein, calcium, potassium, biotin, magnesium, B6, animal fat, vitamin B12, and cholesterol. Factor 2 included 22.15% of total variance and displayed high loadings for selenium, thiamin, carbohydrate, vegetable protein, niacin, sodium, iron, and low intake of vitamin E and vegetable fat. Factor 3 was abundant in fiber, carotene, vitamin C and A.

Table 4, shows the energy-adjusted intakes of nutrients (except energy) based on the nutrient patterns. In the first dietary pattern, the individuals in the first tertile had a significantly higher consumption of carbohydrate, fiber, vegetable protein, fat, vitamin E, selenium, and iron, while the consumption of animal protein, cholesterol, thiamin, riboflavin, pantothenic acid, B6, biotin, folate, B12, sodium, potassium, calcium, magnesium, and zinc was lower in comparison to second and third tertiles.

We found that individuals in the first tertile of second nutrient pattern ate more vegetable fat and vitamin E; however, intake of energy, carbohydrate, fiber, vegetable protein, thiamin, niacin, B6, biotin, folate, vitamin C, sodium, potassium, magnesium, zinc, selenium, and iron was lower.

Participants in the first tertile of the third nutrient pattern had higher consumption of energy, animal protein, fat, cholesterol, niacin, B12, sodium, zinc, and selenium. In contrast, carbohydrate, fiber, vegetable protein, vitamin A, beta carotene, thiamin, pantothenic acid, B6, biotin, folate, vitamin C, potassium, and magnesium intake was low.

In Table 5 we reported the crude and adjusted ORs and 95% CIs for GC across tertiles of nutrient patterns score. Among the three patterns, none of them was correlated to gastric cancer. After controlling for potential confounders, the results did not change materially. Analyses stratified by sex resulted in significant ORs and were presented in Supplementary Tables 2 and 3. By separating sex and considering age and BMI as confounders, the first nutrient pattern was as a risk factor for GC in men (OR= 1.86, 95% CI: 1.03-3.34, p trend=0.04). Further adjustment for age, BMI, *H. pylori* infection, education, and smoking resulted in significant OR in the second tertile of the first nutrient pattern (OR=2.15, 95% CI: 1.13-4.09, p trend=0.02) only in men. We found no significant association across tertiles in the second nutrient pattern and risk of GC.

Discussion

We found a direct association between the first nutrient pattern rich in pantothenic acid, riboflavin, zinc, animal protein, calcium, potassium, and biotin with GC in Iranian men. However, the association was not significant among women.

Despite a strong association between *H pylori* infection and GC, the prevalence of *H-Pylori* infection was lower in patients with gastric cancer than controls in this study. Such findings were previously reported in other case-control studies [25]. This could be attributed to reverse causation in such study designs. We evaluated *H-Pylori* infection by assessing IgG antibodies, which might be eradicated during gastric atrophy and gastric cancer development [26]. In addition, patients with gastric cancer might have received anti *H pylori* treatments, and their infection had eradicated before a diagnosis of gastric cancer [26].

Analysis of nutrient pattern considers all nutrients interactions. It has been used to study the effect of nutrition on the occurrence of several diseases, including diabetes, metabolic syndrome, breast, lung, colorectal, and head and neck cancers [27-30]. However, there is little information linking nutrient pattern and gastric cancer and results are inconclusive [12, 31]. Although a few studies assessed the association between dietary factors and risk of GC in Iran [32-36], none of them used factor analysis in the previous studies. Our first dietary pattern was mostly represented by nutrients that can be found in animal products. In the earlier studies, intake of milk and its products increased the risk of GC [32, 36]. Milk is a major source of calcium, animal protein and riboflavin so one reason for increasing GC risk by first nutrient pattern may be the high-level content of these nutrients. Meats and their products are major sources of nitrosamine compounds that may increase the risk of GC, and some nutrients like animal protein, fat, and B12 can be representative of meat products in the first pattern. Other studies showed an association between animal fat and cholesterol intake and risk of GC [37, 38]. Fat intake may increase weight, reflux, and inflammation, which may increase vulnerability to GC [39, 40]. In agreement with our results, Bertuccio et al., in a case-control study, reported that adherence to animal products pattern containing high levels of animal protein, cholesterol, calcium, zinc, and riboflavin increased GC risk. However, adherence to vitamins and fiber patterns dominated by potassium, folate, vitamin C, beta carotene equivalents, and total fiber did not affect gastric cancer risk in Italy [12]. Vitamins integrated with one-carbon metabolism, including folate, cobalamin, B6, niacin, and riboflavin, are presented in the first nutrient pattern. These are necessary for DNA replication, DNA repair, and regulation of gene expression. There is no consensus on the role of nutrients involved in one-carbon metabolism in the risk of GC. In a new prospective study in Melbourne, they observed a positive association between intake of niacin and overall gastric cancer risk [41]; however, existing results are insufficient to support the role of excess intake of vitamins involved in one-carbon metabolism on the reduction of GC risk, and further studies are required.

The second nutrient pattern, containing high levels of selenium, thiamin, carbohydrate, vegetable protein, sodium, and iron that seems to be achieved by the intake of refined carbohydrates like bread, rice, and pulses. The mean consumption of meat is low in Iran, and the major source of iron is grains and pulses [42], so it is expectable that iron is loaded in this nutrient pattern instead of the first one.

Carbohydrate intake can affect insulin secretion and glycemic response. Hyperinsulinemia and hyperglycemia may lead to gastric carcinogenesis by activation of inappropriate inflammatory, oxidative stress, or proliferative pathways [43]. Yao et al., in a systematic review, supported our results and reported that there is no significant relationship between carbohydrate intake and GC risk [44]. We did not consider glycemic index and glycemic load in the present study. The standard approach to evaluate sodium intake is the measurement of sodium in the urine, so this is a limitation in judgment about the presence of sodium in this pattern.

The third nutrient pattern was dominated by fiber, beta carotene, vitamin C and A. This pattern was rich in antioxidant vitamins and low in macronutrients. According to a meta-analysis, vitamin A, C and E reduced the risk of GC [45]. These results are somewhat in agreement with the case-control study of Pelucchi et al., which reported a protective effect of alpha and beta carotene only among men. At the same time, they observed no significant association between GC risk and vitamin

A and C intake [46]. The protective effect of the vitamin-rich pattern that consists of vitamin E, beta carotene, vitamin C, fiber, sugar, and nitrates was seen in a case-control study conducted by Palli et al. [31]. Also, the traditional pattern dominated by total protein, starch, alcohol, and nitrite increased gastric cancer risk. The larger sample size of the present study is their superiority in comparison to our study.

Several mechanisms may explain the role of nutrients on the risk of GC. Vitamins like C and E have antioxidant and free radical scavenging activity. Vitamin C also can inhibit nitrosamine formation and has anti-*Helicobacter pylori* activity [47, 48]. Carotenes can reduce the GC risk by several mechanisms, including protection against oxidative DNA damage as an antioxidant factor [48], induction of apoptosis, and influence on immune response [49]. Fiber intake can reduce cancer risk by countering the carcinogenic effects of N–nitroso compounds [50]. Also, it can modify microbiome–induced production of short-chain fatty acids, which have immunomodulatory and anti-inflammatory properties and increase the intake of biologically active compounds such as phytochemicals and antioxidants [51]. The effect of nutrients relating to one-carbon metabolism may vary in relation to the genetic polymorphisms [52, 53]. In the present study, folate, B12, B6, and riboflavin which are integrated into one-carbon metabolism, were loaded in the first nutrient pattern, which increases GC risk among men.

The present study had several strengths. We used a valid dish-based questionnaire (the DHQ) in this study. Besides, we applied factor analysis and considered interactions between different nutrients. Although we used a hospital-based study, we recruited healthy visitors as controls. Because the disease controls may change dietary habits due to their disease condition, healthy visitors appropriately represent the exposure distribution of the reference populations that generated the GC cases.

On the other hand, we had some limitations in this study. First, we could not recruit controls in the ages older than 70 years. Therefore, the average age of the GC patients was older than controls. However, because the number of subjects in the control group was larger than GC patients, we could control the effect of age in our multivariate analyses and control the confounding effect of age in this analysis. Although the power of this study was sufficient to study the main objectives of this study, we did not have adequate power to perform analysis in women and maybe a null association in this group is justified by small sample size. In addition, we could not study our hypotheses by GC sub-sites (i.e., cardia and non-cardia). Further studies with a larger sample size are needed to explore the role of dietary factors on the risk of GC in Iran.

In conclusion, we found that the first nutrient pattern mainly represented by nutrients found in animal proteins increases the risk of GC among the Iranian population. This study suggests that reducing the intake of meats, dairy, and fast foods may decrease the risk of GC among Iranian male people. Large studies are required to study the association between dietary factors and risk of GC among the Iranian population.

References

1. World Cancer Research Fund. *Stomach cancer How diet, nutrition and physical activity affect stomach cancer risk*. 2019 27 July 2019]; Available from: https://www.wcrf.org/dietandcancer/stomach-cancer.

2. *New Global Cancer Data: GLOBOCAN 2018*. 2018 27 July 2019]; Available from: https://www.uicc.org/news/new-global-cancer-data-globocan-2018.

3. International Agency for Research on Cancer. *Islamic Republic of Iran*. 2018 27 July 2019]; Available from: https://gco.iarc.fr/today/data/factsheets/populations/364-iran-islamic-republic-of-fact-sheets.pdf.

4. Parsonnet, J., et al., *Helicobacter pylori infection and the risk of gastric carcinoma.* New England Journal of Medicine, 1991. **325**(16): p. 1127-1131.

5. Tramacere, I., et al., *A meta-analysis on alcohol drinking and gastric cancer risk.* Annals of oncology, 2011. **23**(1): p. 28-36.
6. Yang, P., et al., *Overweight, obesity and gastric cancer risk: results from a meta-analysis of cohort studies.* European journal of cancer, 2009. **45**(16): p. 2867-2873.
7. D'Elia, L., et al., *Habitual salt intake and risk of gastric cancer: a meta-analysis of prospective studies.* Clinical nutrition, 2012. **31**(4): p. 489-498.
8. Zhang, Z., et al., *Dietary fiber intake reduces risk for gastric cancer: a meta-analysis.* Gastroenterology, 2013. **145**(1): p. 113-120. e3.
9. Bertuccio, P., et al., *Dietary patterns and gastric cancer risk: a systematic review and meta-analysis.* Annals of Oncology, 2013. **24**(6): p. 1450-1458.
10. Mayne, S.T., et al., *Nutrient intake and risk of subtypes of esophageal and gastric cancer.* Cancer Epidemiology and Prevention Biomarkers, 2001. **10**(10): p. 1055-1062.
11. Fang, X., et al., *Landscape of dietary factors associated with risk of gastric cancer: A systematic review and dose-response meta-analysis of prospective cohort studies.* European Journal of Cancer, 2015. **51**(18): p. 2820-2832.
12. Bertuccio, P., et al., *Nutrient dietary patterns and gastric cancer risk in Italy.* Cancer Epidemiology and Prevention Biomarkers, 2009. **18**(11): p. 2882-2886.
13. Jarosz, M., et al., *Effects of high dose vitamin C treatment on Helicobacter pylori infection and total vitamin C concentration in gastric juice.* European journal of cancer prevention: the official journal of the European Cancer Prevention Organisation (ECP), 1998. **7**(6): p. 449-454.
14. Byers, T. and G. Perry, *Dietary carotenes, vitamin C, and vitamin E as protective antioxidants in human cancers.* Annual review of Nutrition, 1992. **12**(1): p. 139-159.
15. Hoang, B.V., et al., *Effect of dietary vitamin C on gastric cancer risk in the Korean population.* World journal of gastroenterology, 2016. **22**(27): p. 6257.
16. Willett W and B. IM, *Foods and nutrients*. 2nd ed. Nutritional epidemiology. 1998: Oxford University Press.
17. Newby, P. and K.L. Tucker, *Empirically derived eating patterns using factor or cluster analysis: a review.* Nutrition reviews, 2004. **62**(5): p. 177-203.
18. Campbell, P.T., M. Sloan, and N. Kreiger, *Dietary patterns and risk of incident gastric adenocarcinoma.* American journal of epidemiology, 2008. **167**(3): p. 295-304.

19. Denova-Gutiérrez, E., R.U. Hernández-Ramírez, and L. López-Carrillo, *Dietary patterns and gastric cancer risk in Mexico.* Nutrition and cancer, 2014. **66**(3): p. 369-376.
20. TOORANG, F., et al., *Validation of Diet History Questionnaire in Assessing Energy and Nutrient Intakes of Iranian Population.* Iranian Journal of Public Health, 2019. **48**(6): p. 1074-1081.
21. Dorosti Motlagh, A. and M. Tabatabaee, *Food composition table.* Tehran: World Nutrition, 2007.
22. Azar, M. and E. Sarkisian, *Food composition table of Iran: National Nutrition and Food Research Institute.* Shaheed Beheshti University, Tehran, 1980.
23. Kim, J.-O. and C.W. Mueller, *Factor analysis: Statistical methods and practical issues*. 1978: sage.
24. Tabrizi, R., et al., *High prevalence of vitamin D deficiency among Iranian population: a systematic review and meta-analysis.* Iranian journal of medical sciences, 2018. **43**(2): p. 125.
25. Helicobacter and C.C. Group, *Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts.* Gut, 2001. **49**(3): p. 347-353.
26. Ekström, A.M., et al., *Helicobacter pylori in gastric cancer established by CagA immunoblot as a marker of past infection.* Gastroenterology, 2001. **121**(4): p. 784-791.
27. Hajizadeh, B., et al., *Nutrient patterns and risk of esophageal squamous cell carcinoma: a case-control study.* Diseases of the Esophagus, 2012. **25**(5): p. 442-448.
28. Malmir, H., et al., *Patterns of nutrients intakes in relation to glioma: A case-control study.* Clinical Nutrition, 2018. **30**: p. 1-8.
29. Khayyatzadeh, S.S., et al., *Nutrient patterns and their relationship to metabolic syndrome in Iranian adults.* European journal of clinical investigation, 2016. **46**(10): p. 840-852.
30. Bravi, F., et al., *Nutrient dietary patterns and the risk of colorectal cancer: a case–control study from Italy.* Cancer causes & control, 2010. **21**(11): p. 1911-1918.
31. Palli, D., A. Russo, and A. Decarli, *Dietary patterns, nutrient intake and gastric cancer in a high-risk area of Italy.* Cancer causes & control, 2001. **12**(2): p. 163-172.
32. Somi, M.H., et al., *Is there any relationship between food habits in the last two decades and gastric cancer in North-Western Iran?* Asian Pac J Cancer Prev, 2015. **16**(1): p. 283-90.
33. Nemati, A., R. Mahdavi, and A. Naghizadeh Baghi, *Case-control study of dietary pattern and other risk factors for gastric cancer.* Health Promot Perspect, 2012. **2**(1): p. 20-7.
34. Pakseresht, M., et al., *Dietary habits and gastric cancer risk in north-west Iran.* Cancer causes & control, 2011. **22**(5): p. 725-736.
35. Mohebbi, M., et al., *The spatial distribution of esophageal and gastric cancer in Caspian region of Iran: an ecological analysis of diet and socio-economic influences.* Int J Health Geogr, 2011. **10**: p. 13.
36. Pourfarzi, F., et al., *The role of diet and other environmental factors in the causation of gastric cancer in Iran--a population based study.* Int J Cancer, 2009. **125**(8): p. 1953-60.
37. Graham, S., et al., *Diet in the epidemiology of gastric cancer.* 1990.
38. Hu, J., et al., *Macronutrient intake and stomach cancer.* Cancer causes & control, 2015. **26**(6): p. 839-847.
39. Ida, S., M. Watanabe, and H. Baba, *Chronic inflammation and gastrointestinal cancer.* Journal of Cancer Metastasis and Treatment, 2015. **1**(3): p. 138-138.
40. O'Doherty, M.G., et al., *Dietary fat and meat intakes and risk of reflux esophagitis, Barrett's esophagus and esophageal adenocarcinoma.* International journal of cancer, 2011. **129**(6): p. 1493-1502.
41. Dugué, P.-A., et al., *Dietary intake of nutrients involved in one-carbon metabolism and risk of gastric cancer: a prospective study.* Nutrition and cancer, 2019. **71**(4): p. 605-614.
42. Haghshenass, M., et al., *Iron-deficiency anemia in an Iranian population associated with high intakes of iron.* Am J Clin Nutr, 1972. **25**(11): p. 1143-6.

43. Lazarevic, K., A. Nagorni, and M. Jeremic, *Carbohydrate intake, glycemic index, glycemic load and risk of gastric cancer.* Central European journal of public health, 2009. **17**(2): p. 75.
44. Ye, Y., et al., *Association between dietary carbohydrate intake, glycemic index and glycemic load, and risk of gastric cancer.* European Journal of Nutrition, 2017. **56**(3): p. 1169-1177.
45. Kong, P., et al., *Vitamin intake reduce the risk of gastric cancer: meta-analysis and systematic review of randomized and observational studies.* PloS one, 2014. **9**(12): p. e116060.
46. Pelucchi, C., et al., *Dietary intake of selected micronutrients and gastric cancer risk: an Italian case-control study.* Annals of oncology, 2008. **20**(1): p. 160-165.
47. Mirvish, S.S., *Effects of vitamins C and E on N-nitroso compound formation, carcinogenesis, and cancer.* Cancer, 1986. **58**(S8): p. 1842-1850.
48. Steinmetz, K.A. and J.D. Potter, *Vegetables, fruit, and cancer. II. Mechanisms.* Cancer Causes & Control, 1991. **2**(6): p. 427-442.
49. Müller, K., et al., *Carotenoids induce apoptosis in the T-lymphoblast cell line Jurkat E6. 1.* Free radical research, 2002. **36**(7): p. 791-802.
50. Møller, M., R. Dahl, and O. Bøckman, *A possible role of the dietary fibre product, wheat bran, as a nitrite scavenger.* Food and chemical toxicology, 1988. **26**(10): p. 841-845.
51. Guillon, F. and M. Champ, *Structural and physical properties of dietary fibres, and consequences of processing on human physiology.* Food research international, 2000. **33**(3-4): p. 233-245.
52. Eussen, S.J., et al., *Vitamins B2 and B6 and genetic polymorphisms related to one-carbon metabolism as risk factors for gastric adenocarcinoma in the European prospective investigation into cancer and nutrition.* Cancer Epidemiol Biomarkers Prev, 2010. **19**(1): p. 28-38.
53. Nan, H.-M., et al., *Effects of dietary intake and genetic factors on hypermethylation of the hMLH1 gene promoter in gastric cancer.* World Journal of Gastroenterology: WJG, 2005. **11**(25): p. 3834.