Iqra Arif
Student ID: 1535520

The role of dietary modification in the prevention of gastric cancer: understanding the evidence and making a suggestion for change

Abstract

There is evidence to suggest that various dietary modifications provide a platform for preventing gastrointestinal cancer. Gastric adenocarcinoma in particular is thought to be largely associated with diet, with figures showing that 51% of cases are solely related to this. Causative foods include salt, saturated fats, processed foods, red meat and alcohol in excessive amounts. Proposed dietary modifications include switching saturated fats for polyunsaturated and vegetable fats, cutting down on sodium and red meat intake and decreasing alcohol consumption. Following a Mediterranean diet plan has been shown to reduce risk due to a high intake of fruits, vegetables and fibre which are proven to have beneficial qualities in the prevention of gastric cancer.

Introduction

The term 'gastrointestinal cancer' comprises the range of cancers affecting the main and accessory organs within the digestive system. Many contributing factors have been identified in this disease, with a substantial evidence base suggesting that diet plays a significant role. Therefore, by modification of dietary habits, it is hoped that the incidence of new cases can be reduced [1].

Examples in the literature of proposed dietary causes of gastrointestinal cancers include: increased intake of processed foods and red meats which can lead to colorectal [2] and pancreatic cancers owing to their carcinogenic effects [3], pickled foods and high alcohol consumption is linked to oesophageal cancer [4, 5] and the latter also to liver cancer [6]. There are also certain foods which have been shown to help reduce the risk of gastrointestinal cancers, for example fruit, vegetables [7] and fibre [8].

Gastric adenocarcinoma, the most frequent type of gastric cancer, is a tumour of epithelial tissue of glandular origin. It may be caused by increased intake of salt, fats, processed foods, alcohol and red meat [9]. In the UK, statistics have shown that 24% of cases of gastric cancer are associated with high salt intake and 36% of cases with lack of adequate fruits and vegetables in patient's diets. A staggering 75% of gastric cancer cases are lifestyle-related, with 51% diet-related, suggesting that altering this may be preventative of this disease [10]. This will form the main focus of this essay.

Dietary causes of Gastric Adenocarcinoma- Reduction to aid Prevention

Salt:

A meta-analysis of all publications related to this subject from 1966 to 2010 showed an overall direct association between diets rich in sodium and cases of gastric adenocarcinoma. Population cohorts were used to look at trends between consumption levels and cancer risk. 7 of 10 cohorts, within the 'high consumption' group, provided a trend of positive correlation, with the correlation being statistically significant in 3 of the cohorts. Moreover, the risk of development increased by 68% with this increased level of salt consumption as compared to the 'moderate' and 'low' consumption groups. 6 of 10 cohorts within the 'moderate consumption' group also showed a positive correlation between consumption and number of cases, with 3 of the cohorts showing a considerably higher risk. Additional analysis showed

pickled foods and salted fish to be two of the main dietary components, of 11 and 13 of the cohorts respectively, which links these foods to causality [11].

The mechanism behind this lies in the damage to the gastric mucosal tissue caused by high sodium intake. Inflammation and increased epithelial proliferation provide an environment for increasing numbers of carcinogens to enter the mucosa [12]. Salt also increases the ability of Helicobacter pylori bacteria to colonise within the gastric mucosa which causes further damage by stimulating the epithelial cells to make reactive oxygen species. The build-up of these species leads to oxidative damage to DNA in the gastric cells, which is the basis for cells to become cancerous [13]. By reducing salt consumption, such serious damage to the gastric mucosa can be avoided, thus decreasing the chances of the above process. The idea of dietary salt reduction in gastric cancer prevention is supported by the 26% increased risk of the 'high consumption' group (68%) as opposed to the risk in the 'moderate consumption' group (42%) in the meta-analysis. These findings may influence those who are already at a high risk of gastric cancer, for various reasons, as well as the general public to modify their diet in order to lower their risk of developing this disease [11].

Fat:

Another recent multi-faceted meta-analysis was used to look at different types of fats and the risk of them causing gastric adenocarcinoma. 95% confidence intervals were used and the summary relative risk (SSR) was calculated using a random effects model. Figure 1 illustrates the results found for each fat type. The first facet involved 14 articles, comprising a total of 18 studies, which were used to compare a high intake of saturated fats with a low intake. The results calculated indicate a significant positive correlation between high saturated fats intake and risk of gastric cancer. The next 12 articles consisting of 16 studies were assessed to compare high and low intake of polyunsaturated fats and the risk of gastric cancer. Both calculations of SSR and 95% confidence interval indicate a significant negative correlation between a high intake of polyunsaturated fats and the risk of gastric cancer. The third facet made use of 11 articles with 14 studies to look at high and low levels of monounsaturated fat intake and the risk of gastric cancer. The results show no direct correlation between intake of monounsaturated fats and the risk of gastric cancer. The final facet in this analysis involved 5 articles consisting of 6 studies to look at high and low levels of consumption of animal and vegetable fats and risk of gastric cancer. These results show a negative correlation between vegetable fat intake and risk of gastric cancer and no direct correlation between animal fat intake and gastric cancer [14].

Type of Fat:	SSR:	95% Confidence Interval:	P value:
Saturated	1.31	1.09 – 1.58	P < 0.001
Polyunsaturated	0.77	0.65 – 0.92	P = 0.003
Monounsaturated	1.00	0.79 – 1.25	P < 0.001
Animal	1.10	0.90 – 1.33	P = 0.13
Vegetable	0.55	0.41 – 0.74	P = 0.12

Figure 1 **Fat Types and Gastric Cancer Risk.** The table shows the calculated ssr, 95% confidence interval and P values for each fat type [14].

The results of this meta-analysis have shown that a high consumption of saturated fats in particular increases risk of gastric adenocarcinoma. This is due to the fact that a high intake of saturated fats leads to obesity. Obesity may cause gastroesophageal reflux due to relaxation of the lower oesophageal sphincter which is a result of pressure from excess

adipose (fatty) tissue. This reflux causes adenocarcinoma of the stomach's cardia, the area below the junction with the oesophagus [15].

Excess adipose tissue also leads to molecular changes, causing increased concentration of growth factors, leading to excess cell division. Inflammation of the increased adipose tissue also increases risk due to influence on carcinogens [16]. By reducing saturated fats in the diet, the risk of gastric cancer may be reduced accordingly. The meta-analysis suggests replacing saturated fats with vegetable and polyunsaturated fats in the diet [15].

Processed foods and red meat:

An increased intake of processed foods and red meats have been shown to be major contributors to the development of gastric adenocarcinoma. A meta-analysis supporting this by Hongcheng et al looks at both of these.

13 case control studies and 4 cohort studies were used. The findings showed that a high dietary intake of red meat provided a 45% increased risk of gastric cancer. The relative risk was calculated at 1.45 and the 95% confidence interval between 1.22-1.73 ($P<0.001$). As this number is above 1, it shows definite positive correlation to increased risk.

17 case controls and 9 cohort studies were used for the meta-analysis of processed meat and gastric cancer. The result showed a relative risk of 1.45 and 95% confidence interval between 1.26-1.65 ($P<0.001$). An analysis of individual items of processed meats was also conducted as shown in figure 2. All processed meats show a strong positive correlation between a high red meat and processed foods intake and gastric cancer. Heterogeneity was not detected for bacon but was for sausage and ham [17].

Processed Food Type:	Relative Risk:	95% Confidence Inter-	P Value:
Beef	1.28	1.04-1.57	P=0.470
Bacon	1.37	1.17-1.61	P=0.695
Ham	1.44	1.00-2.06	P=0.001
Sausage	1.33	1.16-1.52	P=0.012

Figure 2 **Processed Foods and Gastric Cancer Risk.** The table shows the relative risk, 95% confidence interval and P value for each type of processed food individually analysed within the additional study [17].

The above findings can be justified using cell biology. Iron acts as an essential growth factor for Helicobacter pylori [18]. The increased haem iron content in red meat has hyperproliferative effects leading to gastric cancer, and also resulting in the formation of nitrosamines which are carcinogens [19]. The high nitrite content in processed food also facilitates the production of carcinogenic N-nitroso compounds [20]. It has also been found that iron catalyses the formation of hydroxyl radicals, leading to the destruction of immune cells and promoting the growth of cancerous cells. By cutting down on red meat and cutting out processed food, risk of cancer can almost be halved [19].

Increased alcohol consumption:

In a meta-analysis by Tramacere et al, the risk of gastric adenocarcinoma for non-drinkers and those who consume vast amounts of alcohol was compared. A cohort of 15 studies and 44 case-control studies were used. The relative risk was calculated at 1.07 and the 95% confidence interval between 1.01-1.13 ($P=0.488$) for drinkers versus non-drinkers and a

relative risk of 1.20 and 95% confidence interval between 1.01-1.44 (P=0.561) for heavy drinkers. The findings show a positive correlation between high alcohol consumption and gastric cancer but not a strong correlation for moderate drinking and gastric cancer [21].

High alcohol consumption causes gastric cancer by increasing acid secretion, causing mucosal damage. Alcohol is also said to generate free radicals and reactive O2 species (ROS) [22]. The ROS lead to the damage of proteins and DNA via oxidation [23]. Alcohol can also lead to hormonal imbalance and reduction in vitamin reserves leading to promotion of cancer formation [22]. It can also increase protein levels of certain proto-oncogenes, which can transform cells into cancerous ones [24]. Dietary modification to prevent alcohol consumption from causing gastric cancer, ultimately via carcinogenesis, should involve cutting down the amount consumed [22].

Other dietary improvements for preventing Gastric Adenocarcinoma

Further dietary modifications could include switching to a Mediterranean-style diet, which involves large amounts of fruits, vegetables, fibre, olive oil and no more than a low to moderate consumption of wine, all of which have been shown to reduce the risk of gastric cancer [25].

A recent meta-analysis on fibre, fruit and vegetable consumption and the risk of gastric cancer showed that all 3 bear a negative association, proving that they may be beneficial in terms of lowering risk. The risk of stomach cancer with a high consumption of vegetables showed the following results- relative risk: 0.47 and 95% confidence interval between 0.27-0.81. For fruits the results showed a relative risk of 0.53 and 95% confidence interval between 0.30-0.93. In particular, citrus fruits containing vitamin C showed to have a relative risk of 0.69 and 95% confidence interval between 0.52-0.92. For fibre the findings showed a relative risk of 0.47 and 95% confidence interval between 0.28-0.79 [25]. As all these numbers are below one, they show a negative risk association.

Vitamin c prevents cell proliferation and mutations, and inhibits both the development and colonisation of the Helicobacter pylori bacteria [26]. Vitamin C also prevents oxidative damage of the gastric mucosa [27]. Antioxidants present in fruits and vegetables promote apoptosis of cancerous cells and prevent the production of carcinogens. Their absorption into the gastric mucosa serves as protection [28]. Flavonoids present also prevent proliferation and have a chemopreventative effect [29]. Allium vegetables such as garlic are said to inhibit growth of H. pylori and have an anticancerogenic effect [30].

A diet consisting of a high intake of fibre is beneficial against gastric cancer as it has an action of mechanical cleansing, removing carcinogens from the gastric epithelium [31]. It prevents the formation of carcinogenic N-nitroso compounds by removing nitrite in the stomach. It also delays the cell cycle of the cancerous cells, producing an anticancerous effect [32]. Dietary fibre intake has also been said to delay gastric emptying time, this protects the gastric mucosa by reducing the risk of it being in contact with carcinogens due to the increased amount of undigested food held [33]. Oleic acid, the monounsaturated fatty acid of olive oil, is said to have a role in oncogene regulation. It has been said that it transcriptionally supresses the Her-2/*neu* gene which has a role in gastric carcinoma formation [34].

Conclusion

Diet is one aspect in the multi-factorial process combining genetic and environmental elements that can eventually lead to the formation of cancerous cells. However, it is an aspect which can be controlled by the individual. From the literature reviewed, it is clear that

evidence suggests dietary modifications as described can considerably reduce risk of gastric cancer.

References:

1) Abnet Christian C, Corley Douglas A, Freedman Neal D, Kamangar Farin. Diet and Upper Gastrointestinal Malignancies. *Gastroenterology.* 2015; 148(6): Pg 1234-1243.e4

2) Chan DS, Lau R, Aune D, et al. Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. *PLoS One.* 2011; 6(6): e20456

3) Rachael Z Stolzenberg-Solomon, Amanda J Cross, Debra T Silverman, et al. Meat and meat-muagen intake and pancreatic cancer risk in the NIH-AARP cohort. *Cancer Epidemiology, Biomarkers & prevention.* 2007; 16(12): Pg 2664-2675

4) Roerecke M, Shield K.D, Higuchi S, et al. Estimates of alcohol-related oesophageal cancer burden in Japan: Systematic review and meta-analyses. *Bulletin of the World Health Organization.* 2015; 93(5): Pg 329-338C

5) F Islami, J-S Ren, P R Taylor, F Kamangar. Pickled vegetables and the risk of oesophageal cancer: a meta-analysis. *British Journal of cancer.* 2009; 101(9): Pg 1641

6) Schwartz Lauren, Persson E, Weinstein Stephanie, et al. Alcohol Consumption, One-Carbon Metabolites, Liver Cancer and Liver Disease Mortality: e78156. *PLoS One.* 2013; 8(10): e78156

7) Baroudi Olfa, Chaaben Arij, Mezlini Amel, et al. Impact of lifestyle factors and nutrients intake on occurrence of gastrointestinal cancer in Tunisian population. *Tumor Biology.* 2014; 35(6): Pg 5815-5822

8) Dahm Christina, Keogh Ruth, Spencer Elizabeth, et a. Dietary Fiber and Colorectal Cancer Risk: A Nested Case–Control Study Using Food Diaries. *Journal of the National Cancer Institute.* 2010; 102(9): Pg 614-626

9) Van den Brandt Piet A, Goldbohm R Alexandra. Nutrition in the prevention of gastrointestinal cancer. *Best Practice & Research Clinical Gastroenterology*. 2006; 20(3): Pg 589-603

10) Cancer Research UK. *Stomach cancer risk factors.* Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/stomach-cancer/risk-factors#heading-Five. [Accessed 19th January 2016]

11) D'Elia Lanfranco, Rossi Giovanni, Ippolito Renato, et al. Habitual salt intake and risk of gastric cancer: A meta-analysis of prospective studies. *Clinical Nutrition.* 2012; 31(4): Pg 489-498

12) Wang Xiao-Qin, Terry Paul-D, Yan Hong. Review of salt consumption and stomach cancer risk: Epidemiological and biological evidence. *World journal of gastroenterology.* 2009; 15(18): Pg 2204-13

13) Xu Ying, Yan Ying, Hou Ming-Xiao, Liu Yun-En. NaCl pretreatment attenuates *H.pylori*-induced DNA damage and exacerbates proliferation of gastric epithelial cells (GES-1). *Infectious Agents and Cancer.* 2015; 10: Pg 8

14) Han Jun, Jiang Yi, Liu Xiao, et al. Dietary Fat Intake and Risk of Gastric Cancer: A Meta-Analysis of Observational Studies: e0138580. *PLoS One.* 2015; 10(9): e0138580

15) Kim Hee, Kim Nayoung, Kim Hyun, Lee Hye. Relationship between body mass index and the risk of early gastric cancer and dysplasia regardless of Helicobacter pylori infection. *Gastric cancer*. 2015; 18(4): Pg 762-773

16) Hu Jinfu, Vecchia Carlo, Negri Eva, et al. Macronutrient intake and stomach cancer. *Cancer Causes & Control*. 2015; 26(6): Pg 839-847

17) Zhu Hongcheng, Yang Xi, Zhang Chi, et al. Red and Processed Meat Intake Is Associated with Higher Gastric Cancer Risk: A Meta-Analysis of Epidemiological Observational Studies: e70955. *PLoS One.* 2013; 8(8): e70955

18) Epplein Meira, Zheng Wei, Li Honglan, et al. Diet, Helicobacter pylori Strain-Specific Infection, and Gastric Cancer Risk Among Chinese Men. *Nutrition and Cancer*. 2014; 66(4): Pg 550-557

19) Jakszyn Paula, Agudo Antonio, Lujan-barroso Leila, et al. Dietary intake of heme iron and risk of gastric cancer in the European prospective investigation into cancer and nutrition study. *International Journal of Cancer.* 2012; 130(11): Pg 2654-2663

20) Campbell Peter T, Sloan Margaret, Kreiger Nancy. Dietary Patterns and Risk of Incident Gastric Adenocarcinoma. *American journal of epidemiology*. 2008; 167(3): Pg 295-304

21) Tramacere I, Negri E, Pelucchi C, et al. A meta-analysis on alcohol drinking and gastric cancer risk. *Annals of Oncology*. 2012; 23(1): Pg 28-36

22) Ma Seung-Hyun, Jung Woohyun, Weiderpass Elisabete, et al. Impact of alcohol drinking on gastric cancer development according to Helicobacter pylori infection status. *The British Journal of cancer.* 2015; 113(9): Pg 1381-1388

23) Ma Enbo, Sasazuki Shizuka, Shimazu Taichi. Reactive oxygen species and gastric cancer risk: a large nested case–control study in Japan. *European Journal of Epidemiology.* 2015; 30(7): Pg 589-594

24) Zhang Ye, Sun Li-Ping, Xing Cheng-Zhong, et al. Interaction between GSTP1 Val Allele and H. pylori Infection, Smoking and Alcohol Consumption and Risk of Gastric Cancer among the Chinese Population. *PLoS One.* 2012; 7(10): e47178

25) Turati Federica, Rossi Marta, Pelucchi Claudio, et al. Fruit and vegetables and cancer risk: a review of southern European studies. *British Journal of Nutrition.* 2015; 113(S2): Pg S102-S110

26) Fang Xuexian, Wei Jiayu, He Xuyan, 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): Pg 2820-2832

27) Liu Chun, Russell Robert M. Nutrition and gastric cancer risk: an update. *Nutrition Reviews.* 2008; 66(5): Pg 237-249

28) Praud Delphine, Parpinel Maria, Serafini Mauro, et al. Non-enzymatic antioxidant capacity and risk of gastric cancer. *Cancer Epidemiology.* 2015; 39(3): Pg 340-345

29) J L Petrick, S E Steck, P T Bradshaw, et al. Dietary intake of flavonoids and oesophageal and gastric cancer: incidence and survival in the United States of America (USA). *British Journal of Cancer.* 2015; 112(7): Pg 1291-1300

30) Guercio Valentina, Galeone Carlotta, Turati Federica, La Vecchia Carlo. Gastric Cancer and Allium Vegetable Intake: A Critical Review of the Experimental and Epidemiologic Evidence. *Nutrition and Cancer.* 2014; 66(5): Pg 757-773

31) Bravi Francesca, Scotti Lorenza, Bosetti Cristina. Dietary fiber and stomach cancer risk: a case–control study from Italy. *Cancer Causes & Control.* 2009; 20(6): Pg 847-853

32) Zhang Zhizhong, Xu Gelin, Ma Minmin, et al. Dietary Fiber Intake Reduces Risk for Gastric Cancer: A Meta-analysis. *Gastroenterology.* 2013; 145(1): Pg 113-120.e3

33) Brownlee Iain. The impact of dietary fibre intake on the physiology and health of the stomach and upper gastrointestinal tract. *Bioactive Carbohydrates and Dietary Fibre.* 2014; 4(2): Pg 155-169

34) Menendez Javier A, Papadimitropoulou Adriana, Vellon Luciano, Lupu Ruth. A genomic explanation connecting "Mediterranean diet", olive oil and cancer: Oleic acid, the main monounsaturated Fatty acid of olive oil, induces formation of inhibitory "PEA3 transcription factor-PEA3 DNA binding site" complexes at the Her-2/*neu* (*erb*B-2) oncogene promoter in breast, ovarian and stomach cancer cells. *European Journal of Cancer.* 2006; 42(15): Pg 2425-2432