Nutrients and diet quality in gastrointestinal cancers

Moazzen, Sara

DOI:
10.33612/diss.146370190

Chapter 9

Discussion

Chapter 9

General discussion

Discussion

Nutrition and excess calorie intake are known to be major modifiable risk factors for chronic disease such as cancer, including gastrointestinal (GI) cancers [1], yet knowledge gaps and paradoxes continue to exist regarding the effects of specific nutrients on the prevention or progression of cancer. For instance, despite the observed beneficial effects of vitamins such as dietary folate in preventing GI cancers, supplementation with folic acid and iron is controversial and may increase risk [2]. This is compounded by inconclusive findings on the role of diet quality in the prevention of GI cancer, as quantified by various diet quality indicators [3-7]. There is also limited evidence of diet quality status among GI cancer survivors, which in turn, further hampers strategies to optimize nutritional interventions that seek to improve the prognosis following surgical resection, chemotherapy, and radiotherapy [8].

It is critical that we investigate the roles of specific vitamins and minerals on GI cancer risk, particularly folic acid and iron supplementation. Moreover, the effect of diet quality on the prevention of GI cancer needs to be investigated further. Better understanding the impact of diet quality on GI cancer in patients and survivors may lead to better enteral or parenteral nutrition during therapy, helping to improve not only nutritional needs but also their cancer prognosis. These topics were investigated in this thesis.

Nutrients and GI Cancers

In a systematic review and meta-analysis of 22 observational studies presented in **Chapter 2**, we found that a high intake of total folate in GI cancer subgroups was associated with a decreased risk of colorectal cancer (CRC). However, neither supplementary folic acid nor the blood folate level significantly affected that risk. This pooled analysis contributed more reliable findings compared with a previous meta-analysis that failed to show a significant effect of dietary folate on CRC with fewer numbers of included studies [9]. Nevertheless, the true effect of dietary folate on CRC may be obscured in observational studies due to confounding by healthy behaviors (e.g., other dietary factors and lifestyle), which improve in individuals with higher total folate intake. The observed discrepancies between the current findings and those of the previous meta-analysis [9] could also be explained by genetic variation within study populations modifying the effect of total folate on the risk of CRC [10]. Variation in the methods applied for the assessment of total and dietary folate intake may play a role in observed controversies in findings. We found a null effect on CRC risk of folic acid supplementation and elevated levels of red blood cell folate, but that there was a significantly increased risk of CRC at higher plasma folate levels. Although serum/plasma folate levels are representative of folate/folic acid intake, it is not feasible to distinguish dietary folate and synthetic folic acid using these biomarkers. Given the differences between folate and folic acid metabolism in the body, as well as their effects on CRC, these findings should be interpreted with caution. Notably, in **Chapter 2**, inconsistency in the definition of high folate status contributed to the marked heterogeneity in findings concerning folic acid and CRC risk that was compounded by short follow-up times, the combination of folic acid with other vitamins, and the use of adjunctive aspirin. Together, these may have camouflaged the true effect of folic acid on CRC risk.

Through a population-based ecological study, we found that long term fortification with folic acid and iron was not accompanied by consistent changes in upper gastrointestinal (UGI) cancer incidence, as presented in **Chapter 3**. Increased age-adjusted incidence rates for CRC were detected after fortification with folic acid and iron. In contrast to the observed null effect of long-term flour fortification with folic acid on UGI cancer rates, the pooled results demonstrated a beneficial effect of dietary folate intake and high levels of serum folate on UGI cancer risk [11,12]. This controversy may be due to the differences between the metabolism of synthetic folic acid and dietary folate. Moreover, despite the crucial role of folate in promoting DNA synthesis, repair, and methylation, leading to decreased risks of GI cancers, folic acid might exert a carcinogenesis effect by altering DNA methylation levels [13,14]. It should be noted that folic acid fortification in our study was accompanied by iron, and that this could have altered the observed effect. Based on findings of this thesis, we conclude that national folic acid fortification may not adversely affect the risk of UGI cancer. The inconsistent change in UGI cancer rates after long-term iron fortification was not in line with previous findings on the undesired effect of iron supplementation on GI cancer [15,16]. This may be due to a lower iron status in our study population prior to fortification, which in turn may have inhibited

excess iron intake after fortification. Although fortification with both folic acid and iron appears to increase the rate of CRC, further research is needed before we can make a definitive conclusion.
In the population-based case-control study presented in **Chapter 4**, we proceeded to test whether maternal folic acid supplement intake was associated with CRC risk in a region with long-term folic acid fortification. We found no association. However, in contrast to these findings, beneficial effects on CRC prevention were reported with folic acid supplementation (3 mg/day for 36 months) among subjects who were confirmed to be without colorectal adenomas at recruitment, as well as for those receiving supplemental folic acid combined with vitamins B_6 and B_{12} [17,18]. It should be noted that the results in these latter studies may have been affected by the lower generalizability of the study populations and by modification of the effect of folic acid supplementation by other vitamins. The methods in **Chapter 3** & **Chapter 4** were limited by a lack of information on folate and iron statuses, alcohol intake, and physical activity, which impaired the quality of findings on the association between folic acid fortification/supplementation and GI cancer risk. Besides, inconsistent coverage in the cancer registry systems during the study period in **Chapter 3** required an adjustment of the reported incident cases for the coverage rate of corresponding years.

Folic acid fortification and CRC

There was a reported non-significant effect of folic acid supplementation on the risk of CRC in a meta-analysis of 13 cohort and randomized control trials (**Chapter 2**), as well as that of maternal folic acid supplementation in a population where supplemental folic acid is prescribed with regular intervals for women of childbearing age (**Chapter 4**). Despite these results, the findings from **Chapter 3** support a probable beneficial role of national folic acid fortification on CRC rates. The dual role of folate in the methylation of some genes, where it leads to cell protection, and in triggering carcinogenesis in others may explain the possible undesirable effect of folic acid intake CRC risk [20]. The inconsistent results in this thesis, combined with the highlighted importance of individualizing the dose and duration of folic acid supplementation, necessitates further investigation into the true role of folic acid supplementation/fortification on the risk of CRC. Future investigations should take into account possible confounding factors, including time sequencing [19] and genetic factors responsible for folate metabolism.

Iron fortification and GI cancers

Findings from this thesis (**Chapter 3**) and previous studies [15,16,21] support the possibility that iron supplementation increases susceptibility to CRC. Excess iron intake may induce a systematic oxidative stress response that enhances susceptibility to carcinogenesis. Additionally, combining iron supplementation with folic acid might enhance the iron-induced peroxidation process [22]. Further investigations are required to establish the effect of population-based iron supplementation on the risk of GI cancer.

Diet Quality and GI Cancer

In a systematic review and meta-analysis of related studies, resulting in a sample of approximately 1.5 million individuals (**Chapter 5**), we found that a high-quality diet was significantly and consistently associated with a lower risk of UGI cancer. However, the quality of the pooled findings was insufficient to develop dietary recommendations for preventing UGI cancer.

The observed benefits of a high-quality diet, as quantified by the Diet Inflammatory Index (DII), on UGI cancer prevention contradicted the evidence that there would be no impact on risk [23]. The paucity of food components applied for quantifying diet quality, failure to adjust for risk factors of UGI cancer (e.g., gastroesophageal reflux disease and Helicobacter pylori), and reduced study power due to the previous cohort study (e.g., few incident cases) likely account for the discrepancies. The low overall quality of our findings hampers our ability to develop dietary recommendations for UGI cancer prevention based on the DII scoring system. The main limiting factors were observed inconsistency, indirectness (few studies from some continents, including Asia and North America), publication bias, and diversity in the scoring system based on the inflammatory response of food components.

The desirable effect of a high-quality diet based on the Mediterranean Diet Score (MDS) in terms of UGI cancer prevention has not been confirmed, with studies reporting a non-significant effect of diet quality [23-26]. This discrepancy can be explained in several ways: i) the variation in UGI cancer subgroups in these studies; ii) inter-tumor heterogeneity and not considering confounders such as gastroesophageal reflux disease [24] or H. pylori [24,25] in adjustments; iii) the low number of incident cases [23]; and iv) applying a single nutrition quality assessment tool [24,26].

In the systematic review and meta-analysis of 38 studies presented in **Chapter 6**, we demonstrated a consistent and significant association between high diet quality and lower CRC risk among approximately 5.6 million people. However, a low quality of evidence was observed for the pooled findings.

The controversial findings on the role of high diet quality measured by the DII on CRC prevention shown in this and previous investigations [27-29] may have several explanations. These include the lack of data on food parameters with anti-inflammatory effects in the DII calculation, limitations in adjusting for confounders such as a history of NSAID intake [27], and the poor generalizability of findings due to the study population (e.g., health professionals [28] or individuals with Lynch syndrome [29]).

Given that the protective effect of a low DII-based (i.e., a high anti-inflammatory) diet has been shown consistently in analyses stratified by study design, geographic region, gender, and tumor site, the observed benefit is more likely to be genuine rather than being due to confounding.

In contrast to our findings, several studies reported no benefits from high MDS scores on CRC prevention. Differences in study populations (e.g., use of a specific socioeconomic class that is not truly representative of a general population) [30-34] or the inclusion of a small number of incident cases [31] may have contributed to the high level of heterogeneity. Thus, inconstancies in the existing evidence mean that the efficacy of adhering to a diet based on high MDS scores could not be generalized

in CRC prevention.
The observed benefits of high diet quality, as quantified by the Dietary Approach to Stop Hypertension (DASH), are consistent with current evidence [30,32,35-37]. Nevertheless, the findings were mostly limited to North America, and the small effect size led to a possible indirectness in the overall beneficial findings. This resulted in a down-rating of the overall quality and transparency of the conclusions for developing dietary recommendations.
As a methodological consideration in **Chapter 5** & **Chapter 6**, limiting the findings to a specific geographic region precluded wider generalizability. For example, the preventive effect of high adherence to the Healthy Eating Index (HEI) on CRC risk was consistent in analyses stratified by study design, geographic region, gender, and tumor. Nonetheless, given the limited findings from regions other than North America, and given the observed moderate publication bias despite the use of a homogenous scoring system, we cannot develop recommendations until data are available from large prospective studies from various geographic regions.
We conducted a large population-based prospective study with a median follow-up of 8 years (interquartile range = 2 years) (**Chapter 7**). In this, high diet quality quantified by the Lifeline diet (LLD) and American Cancer society score (ACS) indices was significantly associated with a reduced risk of CRC. The association was driven by a synergy among included food components rather than by any specific food component in either index. These findings were also in agreement with those from pooled findings on the benefits of a high diet quality quantified by various diet quality indices for preventing CRC in **Chapter 6**. Moreover, the performance of the LLD and ACS indices for CRC risk prediction in the Dutch population were highly significant, having comparable effect sizes (1.6-times reduced risk of GI cancer) despite a shorter follow-up time (i.e., approximately half the mean follow-up in pooled findings). In **Chapter 7**, low statistical power was ultimately found given the limited number of UGI cancers, thereby limiting the detection of some hypothesized associations.
Among survivors of GI cancer, the intake of foods with proven desirable health effects did not meet the amounts recommended in dietary guidelines, while food components with undesirable health effects were reportedly ingested on a daily routine basis (**Chapter 8**). Unhealthy foods, including sugar-sweetened beverages, hard margarine, red meat, and processed meat, were consumed in at least one serving per day. According to dietary guidelines, iIt is preferred that these food components not be consumed at all [38]. These findings are consistent with those reported by Zhang et al., who reported a high intake of empty calories, saturated fatty acids, and poor micronutrient intake among survivors of all cancer types [39]. However, some data in **Chapter 8** was self-reported, including that concerning GI cancers, which may have affected the accuracy of the findings.
Additionally, a lack of data on persistent changes in diet quality highlights the possibility of survivor bias in observed diet quality.

Diet Quality and GI Cancer Prevention

The findings on diet quality and UGI cancer risk (**Chapter 5**) are mainly limited to Europe. Thus, further investigation is warranted in other geographic areas to assess the impact of geography. Current findings indicate that gender and tumor type were not responsible for the observed discrepancies because the observed beneficial effects persisted after the analyses were stratified by these variables. Inter-tumoral heterogeneity and differences in the covariates in the included studies remain potential sources of heterogeneity. Furthermore, analysis of CRC risk and diet quality quantified by DASH (**Chapter 6**) was mainly limited to North America and only demonstrated a small effect size. The inclusion of food components with a prominent role in reducing CRC risk, and setting gender, age, and physical activity standards, means that there is higher transparency for developing dietary recommendations to prevent CRC based on DASH compared with the DII, MDS, and HEI. Accordingly, there is a need for further large-scale prospective studies from various geographic regions to improve the quality of evidence on diet quality measured by DASH. This could facilitate the development of meaningful dietary recommendations for the prevention of CRC. In **Chapter 7**, the performance of various nutritional indices at predicting the risk of CRC revealed that using the LLD and ACS nutrition quality indicators could lead to significant CRC prevention in the Dutch population. Null findings on indices specific to cancer prevention demonstrate that there is a demand for nutrition quality indices that are tailored to dietary lifestyle habits needed for cancer prevention.

Diet quality in Survivors of GI Cancer

The findings in **Chapter 8** demonstrated that there diet was imbalanced in the study populations, indicating a need for interventions to improve the quality of nutrition among GI cancer survivors. Existing data indicate that an imbalanced diet has the potential to increase susceptibility to chronic disease [40], and given the increased morbidity among cancer survivors than among the healthy population, we must assess the impact of improving diet quality on morbidity and mortality risk. Conducting interventions that enhance diet quality among cancer survivors may promote longer and healthier lives. Given the problems with food ingestion in many GI cancer survivors, however, we may only improve diet quality through personalized palliative care and enteral nutritional supplements delivered by a team of physicians and nutritionists.

Recommendations for Future Research

The following research recommendations are appropriate to address unresolved discrepancies in current evidence on the effect of folic acid and iron supplementation, as well as folate status, on GI cancer risk. Optimized measurement is a missing component of studies into the diets of patients with cancer, with the potential for more precise association estimates if dose-response analyses can be conducted. Such an approach could better define the effects of nutrient levels (e.g., iron and folic acid status/intake) on the risk of GI cancer. Further, a unified pooled analysis by

nutrient intake category could minimize any discrepancies about exposure levels across populations. Another shortcoming of studies conducted into the relationship between diet and cancer to date is that there has been no assessment of the modifying effect of the molecular mechanism of dietary digestion and utilization in the body. Given the possible synergy between genetic susceptibility for GI cancer and its metabolomic fingerprints, together with how this interacts with nutrients [41-46], future studies should investigate the added value of including genetic susceptibility and metabolomic profiles to CRC risk prediction for different levels of nutrients. These shortcomings, coupled with those discussed in the various chapters of this thesis, reveal that there is a low quality of evidence for the effect of a high diet quality on GI cancer.

The current body of evidence is not sufficient to develop scientifically validated dietary guidelines for practical application, despite the growing popular support for a beneficial role of diet in lowering cancer risk. Prospective investigations are therefore warranted to improve the limited evidence on diet quality quantified by general and cancer-specific dietary indices, specifically in less represented regions. In turn, this will contribute to a higher transparency for developing globally valid dietary guidelines for not only preventing, but also for improving the prognosis of, GI cancer. Investigating the genetic and metabolic state of the individual offers an opportunity to fine-tune our understanding of the relationship between nutrients and GI cancers in terms of genetic susceptibility and metabolomic profile. The latter will be crucial to drive effective personalized nutritional advice for the prevention of GI cancer, and indeed, should serve as a key marker on the roadmap to near-future applicable cancer-preventive diet programs.

References

1. Di Luzio, R. et al. Role of nutrition in gastrointestinal oncological patients. Eur Rev Med Pharmacol Sci. 14(4):277-84 (2010).

2. Kim, Y. I. Folate: a magic bullet or a double edged sword for colorectal cancer prevention? Gut. 2006;55(10):1387-9. doi: 10.1136/gut.2006.095463 (2006).

3. Jayedi, A. et al. Dietary Inflammatory Index and Site-Specific Cancer Risk: A Systematic Review and Dose-Response Meta-Analysis. Adv Nutr.1;9(4):388-403. doi:10.1093/advances/nmy015 (2018).

4. Mohseni, S. et al. The beneficial effects of probiotic administration on wound healing and metabolic status in patients with diabetic foot ulcer: A randomized, double-blind, placebo-controlled trial. Diabetes Metab Res Rev. 34(3). doi: 10.1002/dmrr.2970 (2018).

5. Galbete, C. et al. Nordic diet, Mediterranean diet, and the risk of chronic diseases: the EPIC-Potsdam study. BMC Med. 27;16(1):99. doi:10.1186/s12916-018-1082-y (2018).

6. Schwingshackl, L. & Hoffmann, G. Diet quality as assessed by the Healthy Eating Index, the Alternate Healthy Eating Index, the Dietary Approaches to Stop Hypertension score, and health outcomes: a systematic review and meta-analysis of cohort studies. J Acad Nutr Diet. 115(5):780-800.e5.doi:10.1016/j.jand.2014.12.009 (2015).

7. Schwingshackl, L. & Hoffmann, G. Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis of observational studies. Cancer Med. doi:10.1002/cam4.539. doi:10.1002/cam4.539 (2015).

8. Bazzan, A. J. et al. Diet and nutrition in cancer survivorship and palliative care. Evidence-based complementary and alternative medicine. Evid Based Complement Alternat Med. 2013:917647. doi:10.1155/2013/917647 (2013).

9. Sanjoaquin, M. A. et al. Folate intake and colorectal cancer risk: a meta-analytical approach. Int J Cancer. 20;113(5):825-8. doi: 10.1002/ijc.20648 (2005).

10. Kim, J. et al. Dietary intake of folate and alcohol, MTHFR C677T polymorphism, and colorectal cancer risk in Korea. Am J Clin Nutr. 95(2):405-12. doi: 10.3945/ajcn.111.020255 (2012).

11. Zhao, Y. et al. Folate intake, serum folate levels and esophageal cancer risk: an overall and dose-response meta-analysis. Oncotarget. 7;8(6):10458-10469. doi: 10.18632/oncotarget.14432 (2017).

12. Liu, W. et al. Associations between dietary folate intake and risks of esophageal, gastric and pancreatic cancers: an overall and dose-response meta-analysis. Oncotarget. 28;8(49):86828-86842. doi: 10.18632/oncotarget.18775 (2017).

13. Blount, B. C. et al. Folate deficiency causes uracil misincorporation into human DNA and chromosome breakage: implications for cancer and neuronal damage. Proc Natl Acad Sci U S A. 1;94(7):3290-5. doi: 10.1073/pnas.94.7.3290 (1997).

14. Choi, S. W. & Mason, J. B. Folate and carcinogenesis: an integrated scheme. J Nutr. 130(2):129-32. doi: 10.1093/jn/130.2.129 (2000).

15. Fonseca-Nunes, A. et al. Iron and Cancer Risk—A Systematic Review and Meta-analysis of the Epidemiological Evidence. Cancer Epidemiol Biomarkers Prev. 23(1):12-31. doi: 10.1158/1055-9965 (2013).

16. Corley, D. A. et al. Iron Intake and Body Iron Stores as Risk Factors for Barrett's Esophagus: A Community-Based Study. Am J Gastroenterol. 103(12):2997-3004. doi: 10.1111/j.1572-0241.2008.02156.x (2008).

17. Gao, Q.Y. et al. Folic acid prevents the initial occurrence of sporadic colorectal adenoma in Chinese older than 50 years of age: a randomized clinical trial. Cancer Prev Res. 6(7):744-52. doi: 10.1158/1940-6207.CAPR-13-0013 (2013).

18. Song, Y. et al. Effect of combined folic acid, vitamin B6, and vitamin B12 on colorectal adenoma. J Natl Cancer Inst. 17;104(20):1562-75. doi: 10.1093/jnci/djs370 (2012).

19. Gibson, T. M. et al. Pre-and postfortification intake of folate and risk of colorectal cancer in a large prospective cohort study in the United States. Am J Clin Nutr. 94(4):1053-62. doi: 10.3945/ajcn.110.002659 (2011).

20. Kim, Y. I. Folate and colorectal cancer: an evidence-based critical review. Mol Nutr Food Res. 51(3):267-92. doi: 10.1002/mnfr.200600191 (2007).

21. Wurzelmann, J. I. et al. Iron intake and the risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev. 5(7):503-7 (1996).

22. Pellis, L. et al. High folic acid increases cell turnover and lowers differentiation and iron content in human HT29 colon cancer cells. Br J Nutr. 99(4):703-8. doi: 10.1017/S0007114507824147 (2008).

23. Boden, S. et al. The inflammatory potential of diet in determining cancer risk; A prospective investigation of two dietary pattern scores. PLoS One. 12;14(4):e0214551. doi: 10.1371/journal.pone.0214551 (2019).

24. Li, W. et al. Index-based Dietary Patterns and Risk of Esophageal and Gastric Cancer in a Large Cohort Study. Clin Gastroenterol Hepatol. 11(9):1130-1136.e2. doi: 10.1016/j.cgh.2013.03.023 (2013).

25. Buckland, G. et al. Healthy lifestyle index and risk of gastric adenocarcinoma in the EPIC cohort study. International Journal of Cancer.1;137(3):598-606. doi:10.1002/ijc.29411 (2015).

26. Wang, C. et al. Diet Quality Scores and Risk of Nasopharyngeal Carcinoma in Chinese Adults: A Case-Control Study. Nutrients. 25;8(3):112. doi:10.3390/nu8030112 (2016).

27. Boden, S. et al. The inflammatory potential of diet in determining cancer risk; A prospective investigation of two dietary pattern scores. PLoS One. 12;14(4):e0214551. doi:10.1371/journal.pone.0214551 (2019).

28. Liu, L. et al. Association Between Inflammatory Diet Pattern and Risk of Colorectal Carcinoma Subtypes Classified by Immune Responses to Tumor. Gastroenterology. 153(6):1517-1530.e14. doi:10.1053/j.gastro.2017.08.045 (2017).

29. Brouwer, J. G. et al. Inflammatory potential of the diet and colorectal tumor risk in persons with Lynch syndrome. Am J Clin Nutr.106(5):1287-1294. doi:10.3945/ajcn.117.152900 (2017).

30. Torres Stone, R. A. et al. The association of dietary quality with colorectal cancer among normal weight, overweight and obese men and women: a prospective longitudinal study in the USA. BMJ Open. 5;7(6):e015619. doi:10.1136/bmjopen-2016-015619 (2017).

31. Lavalette, C. et al. Cancer-Specific and General Nutritional Scores and Cancer Risk: Results from the Prospective NutriNet-Sante Cohort. Cancer Res. 1;78(15):4427-4435. doi:10.1158/0008-5472.can-18-0155 (2018).

32. Petimar, J. et al. Recommendation-based dietary indexes and risk of colorectal cancer in the Nurses' Health Study and Health Professionals Follow-up Study. The American Journal of Clinical Nutrition. 1;108(5):1092-1103. doi:10.1093/ajcn/nqy171 (2018).

33. Bamia, C. et al. Mediterranean diet and colorectal cancer risk: results from a European cohort. European journal of epidemiology 28, 317-328. doi:10.1007/s10654-013-9795-x (2013).

34. Fung, T. T. et al. The Mediterranean and Dietary Approaches to Stop Hypertension (DASH)

diets and colorectal cancer. The American Journal of Clinical Nutrition. 92(6):1429-35. doi:10.3945/ajcn.2010.29242 (2010).

35. Park, S. Y. et al. High-Quality Diets Associate With Reduced Risk of Colorectal Cancer: Analyses of Diet Quality Indexes in the Multiethnic Cohort. Gastroenterology.153(2):386-394.e2doi:10.1053/j.gastro.2017.04.004 (2017).

36. Miller, P. E. et al. Comparison of 4 established DASH diet indexes: examining associations of index scores and colorectal cancer. Am J Clin Nutr. 98(3):794-803. doi:10.3945/ajcn.113.063602 (2013).

37. Erben, V. et al. Dietary patterns and risk of advanced colorectal neoplasms: A large population based screening study in Germany. Preventive Medicine. 111:101-109, doi:10.1016/j.ypmed.2018.02.025 (2018).

38. Kromhout, D. et al. The 2015 Dutch food-based dietary guidelines. European journal of clinical nutrition. 70(8):869-78. doi:10.1038/ejcn.2016.52 (2016).

39. Zhang, F. F. et al. Diet quality of cancer survivors and noncancer individuals: Results from a national survey. Cancer. 1;121(23):4212-21. doi:10.1002/cncr.29488 (2015).

40. Guinter, M. A. et al. Associations of Pre- and Postdiagnosis Diet Quality With Risk of Mortality Among Men and Women With Colorectal Cancer. J Clin Oncol, 19;36(34):JCO1800714. doi:10.1200/jco.18.00714 (2018).

41. Irimie, A. I. et al. Role of Key Micronutrients from Nutrigenetic and Nutrigenomic Perspectives in Cancer Prevention. Medicina (Kaunas).18;55(6):283. doi:10.3390/medicina55060283 (2019).

42. Nilsson, P. D. & Newsome, J. M. Prioritization of Variants for Investigation of Genotype-Directed Nutrition in Human Superpopulations. 18;20(14):3516. doi:10.3390/ijms20143516 (2019).

43. Bultman, S. J. Interplay between diet, gut microbiota, epigenetic events, and colorectal cancer. Molecular nutrition & food research 61(1):10.1002/mnfr.201500902. doi:10.1002/mnfr.201500902 (2017).

44. Gargallo-Puyuelo, C. J. et al. Adding genetic scores to risk models in colorectal cancer. Oncotarget 6;10(47): 4803-4804. doi:10.18632/oncotarget.27110 (2019).

45. Murphy, N. et al. A Nested Case-Control Study of Metabolically Defined Body Size Phenotypes and Risk of Colorectal Cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). PLoS medicine 5;13(4):e100198. doi:10.1371/journal.pmed.1001988 (2016).

46. Song, M. et al. Nutrients, foods, and colorectal cancer prevention. Gastroenterology 148(6):1244-60.e16. doi: 10.1053/j.gastro.2014.12.035 (2015).