Nutrients and diet quality in gastrointestinal cancers

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Chapter 1

General Introduction

The evident role of nutrients and dietary patterns in the risk of complex chronic diseases has led to the global notion of diet quality indicators and dietary interventions as a primary tool to prevent chronic diseases and promote health status [1-3]. Accordingly, recent evidence-based strategies recommend an increased daily intake of plant-based dietary components and a restriction of the intake of red and processed meats and sugar-sweetened beverages in the prevention and even treatment of coronary heart disease, stroke, and type 2 diabetes as well as cancers [3]. An accumulating body of evidence suggests a notable role for dietary modifications based on food components in gastrointestinal (GI) cancers prevention and prognosis [4,5]. However, findings from population-based investigations on the beneficiary effect of specific food components, including folic acid, iron, as well as that of various diet quality indicators on GI cancers risk and survivorship, are still controversial [6-8].

Gastrointestinal cancers epidemiology

GI cancers are an umbrella term for a group of malignancies affecting the digestive system, including esophagus, gastric, and colorectal cancers [9]. As the first most prevalent cancer types and the second leading cancer cause of mortality worldwide, GI tract cancers affect ~3.5 million new cases with~2.2 million cancer-specific deaths annually, **Figure 1A** [10]. Among genetically susceptible individuals, environmental predispositions as modifiable factors play a crucial role in the pathogenesis of GI cancers, their progression, and prognosis [9]. Nutrients and dietary habits such as excessive calorie intake leading to adiposity, sedentary lifestyle, smoking, and excess alcohol drinking are the foremost common environmental factors affecting the risk for GI cancers as well as cancer prognosis [9]. In some European countries, early diagnosis, together with high-quality treatment procedure, improvement in lifestyle, and diet, has led to a substantial increase in cancer survival rates [11].
In the Netherlands, a ~20% increase in five years survival rates were reported for esophagus and gastric cancers and colorectal cancers within the past three decades, **Figure 1B** [12].

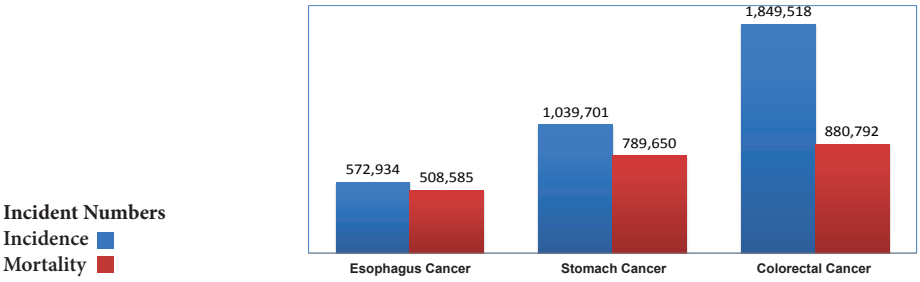

Figure 1A: Worldwide gastrointestinal cancers incident and mortality numbers in 2018 [10].

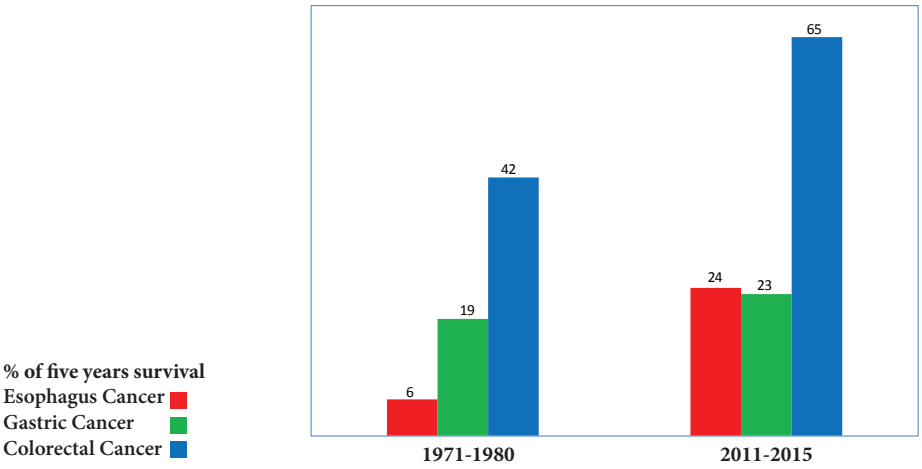

Figure 1B: Percentage of five years of gastrointestinal cancers survival among prevalent cases in two periods of 1971-1980 and 2011-2015 in the Netherlands [12].

Nutrients, bioactive food components, foods, and diet

Nutrients, such as proteins, carbohydrates, fats, vitamins, and minerals, as the main components of the foods, are essential substances in energy provision, cellular proliferation, as well as regulation of chemical processes within the body [13].
In addition to nutrients, foods also contain other, no-energetic, bioactive compounds, including phytochemicals and fiber. Diet, in turn, is defined as the sum of the foods that an individual habitually ingests [14].

Nutrients, bioactive food components, and foods in the prevention of GI cancers

The effect of micronutrients (i.e., natural vitamins and minerals or synthesized vitamins), macronutrients, and other bioactive food components on various subtypes of GI cancers risk has been extensively assessed. For instance, systematic analyses of World Cancer Research Fund International revealed limited, and yet inconclusive findings on the role of vitamins A, C, E, B_1, B_2, B_9 as well as the role of calcium, zinc, carotenoids, proteins, lipids in the prevention of esophagus [7], gastric [6] and, colorectal cancers [5]. On the contrary, strong evidence exists on the probable beneficiary role of calcium and fiber in colorectal cancer prevention, i.e., a 10% reduction in risk of colorectal cancer per 300 mg/day increase in calcium intake and 10 gr/day increases in fiber intake has been observed [4]. Also the detrimental effect of high sodium intake on gastric cancer has been well established [15]. Additionally, findings suggest probable adverse effects for synthesized, folic acid, and iron in GI cancers risk, leading to controversies across studies [16-21]. While the preventive role of restricted sodium intake on chronic disease, including GI cancers, has been extensively investigated, the effect of long-term folic acid and iron supplementation on cancers of the GI is assessed rarely. Thus, an ongoing dispute exists on the safety of population-based folic acid and iron supplementations, as a strategy to compensate for deficiencies of these nutrients [19,22,23]. Furthermore, the interaction between nutrients might lead to altered associations between micronutrient intake and GI cancers risk [24].
Nevertheless, limited findings exist on the association between folic acid and iron supplementation, when ingested simultaneously, and risk for GI cancers.
To assess the effect of the simultaneous intake of nutrients, the role of single foods, which are composed of different nutrients and bioactive components in the prevention of GI cancers have been investigated. Based on recent reviews and analyses on single foods and GI cancers, a strong level of evidence confirms the adverse effect of alcoholic drinks on GI cancers [5-7]. Where limited findings suggest an undesired effect for processed meat on esophagus cancers risk [7], the role of processed meat in the development of gastric and colorectal cancer is confirmed [5,6]. It is estimated that a 100 gr/day increase in red and processed meat intake leads to a 16% increase in the risk of colorectal cancer[4]. Limited evidence demonstrates the preventive effect of fruit and vegetable intake on GI cancers [5-7]. Meanwhile, a strong level of evidence confirms the beneficiary role of whole grains, dietary fiber, and dairy products in colorectal cancer prevention [5]. The role of foods with a high content of vitamin C, D, and multivitamin supplements in the prevention of colorectal cancers has been confirmed by limited evidence [5].

Diet quality in the prevention of GI cancers

Diet quality is mainly assessed by data-driven and hypothesis-driven methods. In the data-driven approach, the diet quality is characterized by the main dietary components within populations, which in turn describes diet quality based on dietary habits of the study population. Findings based on data-driven methods show limited evidence for a desirable impact of improved diet quality in the prevention of GI cancers [5-7]. On the other hand, hypothesis-driven, known as dietary indices, quantify the diet quality by comparing the actual intake of nutrients or food groups with the reference intake, which are defined based on the evident role of food components in the prevention of common chronic disease. The Diet Inflammatory Index, Mediterranean Diet Score, Diet Approach to Stop Hypertension, and Healthy Eating Index, with a different foundation and different food components, are commonly applied to quantify the quality of diet in nutrition-epidemiological studies, **Box 1**. Controversial findings have been reported on diet quality quantified by existing dietary indices in the prevention of GI cancers [25]. Therefore, the results on the beneficiary role of diet quality quantified by indices in the prevention of GI cancers are inconclusive.

Box 1: The dietary indices used to quantify diet quality

Diet quality index	Origin of the index	Included food components
DII	Based pro/anti-inflammatory association of dietary components with inflammatory biomarkers, including IL-1β, IL -4, IL-6, IL-10, TNF-α	Includes 19–45 dietary components *Pro-inflammatory components*: Carbohydrate, Protein, total fat, Saturated fatty acids, Cholesterol, Vitamin B12, Fe, Alcohol Energy. *Anti-inflammatory components*: Onion, Saffron, Garlic, Ginger, Fiber, Folic acid, Caffeine, MUFA, PUFA, n-3 fatty acids, n-6 fatty acids, Niacin, Riboflavin, Vitamin B6, β carotene, Mg
MDS	Based on the evident role of foods components in cardiovascular health	Includes 8–11 food components: *Foods with beneficiary effects*: Cereals, vegetables, Fruits, Legumes, Nuts, Olive Oil, Fish, High ratio of MUFA+PUFA /SFA. *Foods with adverse effect*: Milk and dairies, Meat and processed products, sweets, sweetened beverages, Saturated fatty acids, Cholesterol, Alcoholic beverages, Alcohols (consuming (alcohol >50 gr/day alcohol)
DASH	Based on evidence on diet elements related to hypertension management	*Food groups*: Fruits, Vegetables, Red meat, low-fat dairies, Sugar-sweetened beverages, Oils, Whole grains, Nuts, and Legumes.
HEI	Based on healthy eating guidelines without a specific mechanism	*Foods with beneficiary effect*: Fruits, Vegetables, Whole grain, beans, Dairy, Total protein in food, seafood, PUFA+MUFA/SFA≥2.5 *Foods with adverse effect*: Sodium, Empty calorie, refined grains, PUFA+MUFA/SFA < 1.2

Abbreviations: DASH, Dietary Approach to Stop Hypertension; DII, Diet Inflammatory Index; HEI, Healthy Eating Index; IL, Interleukin; MDS, Mediterranean Diet Score; Mg, Magnesium; MUFA, Mono Unsaturated Fatty Acids; PUFA, Poly Unsaturated Fatty Acids; SFA, Saturated Fatty Acids.

GI carcinogenesis etiology

The etiology of GI cancers consists of molecular-based pathways in GI cancer progression, including; inflammation and oxidative stress, genomic instability, telomere shortening, impaired DNA repair system, polyamine metabolism, and activation-induced cytidine deaminase [28].

Nutrient and foods involved mechanisms in the prevention of GI cancers

Nutrients and foods affect GI carcinogenesis via molecular pathways involved in GI cancers etiology. These pathways include inflammation and oxidative response [4], genome health and stability [27], telomere length protection [28], and proper function of DNA repair system [29]. Specific micronutrients, including Vitamin A, Vitamin C, Vitamin B9, selenium, and fiber, exert their plausible role via reducing DNA damage by scavenging oxygen radicals and inhibiting the expression of carcinogenesis triggering genes [1]. Further, food components, including vitamins B, vitamin D, calcium, omega-3 fatty acids, antioxidant nutrients, inhibit markers of systemic inflammation, and activation of substantial immune signaling pathways [4].
Interestingly, high sodium exerts its detrimental effect on GI cancers risk by disrupting the mucosal barrier, which in turn leads to inflammation, atrophy and, increase immune response, **Figure 2** [15].
Red and processed meat with high hem-iron and nitrate content increase oxidative stress and inflammatory response [30]. Contrary to the undesired effect of red meat, dairies, whole grain, fruits, and vegetables, inhibit carcinogenesis via suppressing inflammation and oxidative stress pathways, boosting the immune system, and decreased epithelial damage [4]. Adiposity, mainly caused by excess energy intake via macronutrients and foods, induces carcinogenesis by enhanced systematic inflammation response, insulin resistance, and angiogenesis, **Figure 2** [31].

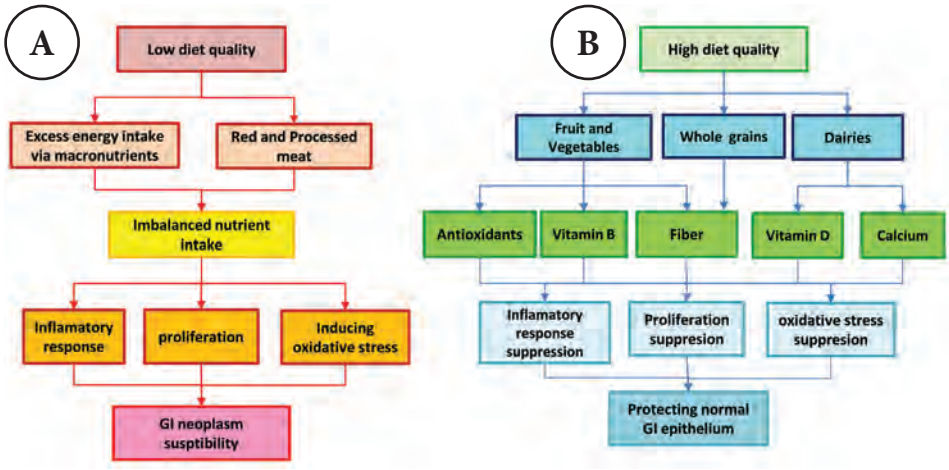

Figure 2: Proposed mechanisms related to the role of nutrients, foods, and diet quality in susceptibility to gastrointestinal cancers neoplasm [32,4,26]. A) The mechanism involved in GI neoplasm susceptibility caused by low diet quality B) The mechanism involved in GI neoplasm susceptibility caused by high diet quality.

Diet quality involved mechanisms in GI cancers prevention

Low diet quality, characterized by low intake of fruits, vegetables, dairies, and high amounts of red/processed meats, and saturated fats, promotes selective proliferation of microbiome subpopulations. In turn, this will lead to the induction of oxidative stress, nontoxicity, host immune response disturbance, and chronic inflammation [33]. High diet quality, mainly consisting of high amounts of fruits, vegetables, whole grains and dairies, and omega-3 fatty acids, on the contrary, leads to a balance in gut microbiota population and hampers inflammation and carcinogenesis, **Figure 2** [34].

Nutrients, foods and diet quality involved mechanisms in GI cancers progression

Given the role of the inflammatory response, and oxidative stress in the progress of GI cancers, proper nutritional interventions in improved cancer prognosis are of high importance. These interventions mainly consist of nutrients and foods, which will lead to reduced oxidative and inflammatory response for patients diagnosed with GI cancers [35]. The role of micronutrients and bioactive foods components, including vitamins A, C, and vitamin D, omega-3 fatty acids, and antioxidants in modulating tumor growth, progression, and metastasis has been demonstrated in the literature [36]. Furthermore, investigations on various combinations of nutrients, mainly with antioxidant effects, have shown a substantial therapeutic efficiency in improved cancer prognosis [37]. Red and processed meats have a probable role in cancer recurrence and mortality, via activating genes responsible for carcinogenesis [38].
Also, foods with high-calorie content such as sweetened beverages, fast foods, and fried foods lead to poor cancer prognosis via their contribution to obesity and diabetes [36].
Likewise, improved diet quality among GI cancer patients/survivors contributes to an enhanced overall quality of life, as well as amended medical conditions [36,37]. Recent evidence indicates a demand for improving diet quality among GI cancers survivors [39]. Nonetheless, related investigations yield inconsistent findings [39-42]. Thus, there is a growing demand to characterize diet quality among these patients, which in turn leads to the well-targeted implementation of dietary interventions.

Thesis objective and outline

Strong evidence confirms the role of several food components and foods, including fiber, calcium, sodium, red, and processed meat in gastrointestinal prevention and progression. Limited, though consistent, findings exist on the effect of foods with a high content of vitamin C, D, and multivitamin supplements in the prevention of GI cancers. Nevertheless, results on the role of supplementation with specific micronutrients, including folic acid and iron in the risk of GI cancers, are controversial. Moreover, the evidence on the effect of diet quality on GI cancers risk and prognosis are inconclusive. The objective of this thesis is to provide evidence on food components and diet quality in GI cancers risk and prognosis, with focus on the effect of long term population-based supplementation of folic acid and iron and that of diet quality in risk for GI cancers and diet quality status among GI cancers survivors. The investigations consist of extended systematic reviews and meta-analyses, registry-

based epidemiologic research, ecological and population-based case-control, and cohort studies. In each of the following chapters, one of the main study questions are answered.

Part 1: Nutrients and gastrointestinal cancers

In **Chapter 2**, I will present our investigation on whether folic acid intake and folate status are associated with reduced colorectal cancer risk. This chapter is a broad systematic review accompanied by a meta-analysis consisting of randomized clinical trials, cohort, and case-control studies, investigating the effect of folic acid supplementation and folate status on colorectal cancer risk.
In **Chapter 3**, the focus is on the potential association between national flour fortification with folic acid and iron on the one hand, and a potentially increased GI cancer occurrence in the population on the other hand. This investigation explored the co-occurrence of long-term population-based food fortification with folic acid and Iron in Iran on the incidence of common cancers of the GI tract. In this study, I measured the cancer occurrence before the fortification period compared to the cancer occurrence after the fortification program was implemented in Iran.
In **Chapter 4**, I questioned whether there is a relationship between long-term folic acid supplement intake and GI cancer risk in women. Together with my collogues, I explored the long-term effects of maternal folic acid supplementation on colorectal cancer risk in a homogeneous study population. Within this chapter, the association in the entire rural population of Azerbaijan province in Iran was specifically assessed. Iran is one of the regions in the world that have applied a nation-wide food fortification with folic acid over ten years.

Passing through the specific question of supplementation/fortification with folic acid and the risk of GI cancers, the focus is turned on to another more general direction; the role of quality of diet in GI cancers risk.

Part 2: Diet quality and gastrointestinal cancers

In **Chapter 5**, the association between high diet quality and the upper gastrointestinal (UGI) cancer risk was investigated. In this chapter, the findings are presented from an extensive, systematic review and meta-analysis of existing data assessing the association between diet quality (as quantified by existing dietary indices, see **Box 1**) and UGI cancers. I evaluated whether there is sufficient evidence of high scientific quality to develop dietary guidelines for the prevention of UGI cancers. Later, the quality of pooled findings was assessed by Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Further, the controversies and knowledge gaps putting into future perspectives are discussed.
In **Chapter 6**, the study question was whether high diet quality measured by priory defined by dietary indices (see **Box 1**) is associated with reduced risk of colorectal cancer. In this chapter, the same strategy with the previous chapter was applied, as the first step, to assess the association of diet quality with the risk of colorectal cancer. In the next step, I evaluated the quality of overall findings per individual dietary indices by GRADE, mainly to explore whether sufficient high-quality evidence exists

to transfer current knowledge to developing dietary guidelines for the prevention and management of colorectal cancer.

In **Chapter 7**, I assessed the effect of diet quality, quantified by general or cancer-specific dietary indices, on GI cancer risk. In this chapter, the long-term effect on diet quality on GI cancers risk was assessed in a population-based cohort setting with a median follow up years of 8 years (Inter quartile range=2years).

In **Chapter 8**, I turned the attention to diet quality among GI cancers survivors, questioning diet quality status among GI cancer survivors with different tumor sites and time since diagnosis. In the next step, I compared these with a cohort of individuals with no history of cancer. To provide clinicians with an overview of diet quality among GI cancer survivors, the adherence to dietary guidelines, and the mean daily intake of food components of diet among these patients are presented.

Finally, in **Chapter 9**, I summarize the major findings of our series of investigations. I put forward the rationale of these findings in the future of diet role in the prevention and management of cancer. Additionally, the knowledge gaps and proposed directions for future investigations on diet and GI cancers prevention and prognosis are highlighted.

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Part 1

Nutrients and gastrointestinal cancers


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