DIETARY PATTERNS COLORECTAL CANCER RISK AND SURVIVAL IN NEWFOUNDLAND, CANADA

by

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ABSTRACT

Diet patterns commonly used in epidemiological research are derived using different methods, yet there have been few studies assessing if and how research results may vary in the same population across diet patterns.

This study assesses and compares five different diet patterns identified by Principal Component Analysis (PCA), Cluster Analysis (CA), Alternate Mediterranean Diet (Alt-Med), Dietary Inflammation Index (DII), and Recommended Food Score (RFS). Colorectal cancer risk and patient's survival is estimated using different patterns as an independent variable. Comparisons are made using hazards ratio, correlation coefficients and distributions of individuals in clusters.

Disease outcome estimation varied with diet patterns used and is mainly attributed to differences in its foundation. Hazards ratios for DFS varied from 1.82; (95% CI- 1.07-3.09) for processed meat pattern identified by PCA to HR 2.19; (95% CI 1.03-4.67) for cluster characterized by meat and dairy products and HR 1.95; (95% CI 1.13-3.37) for cluster characterized by refined grains, sugar, soft drinks. Only cluster characterized by refined grains, sugar, soft drinks had higher risk of OS (HR 2.05; 95% CI 1.18-3.57). All the diet indices showed similar null associations with both DFS and OS except Poor adherence to altMED increased the risk of all-cause mortality (HR 1.62; 95% CI 1.04-2.56).

Key Words: Colorectal cancer, cancer risk, cancer survival, diet patterns

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Alt-Med	Alternative Mediterranean Diet
BMI	Body Mass Index
CA	Cluster Analysis
CRC	Colorectal Cancer
DFS	Disease-Free Survival
DII	Dietary Inflammatory Index
FHQ	Family History Questionnaire
ICD	International Classification of Disease
IL	Interleukins
FFQ	Food Frequency Questionnaire
METs	Metabolic Equivalent of Task
MUFA	Mono Unsaturated Fatty Acid
NFCCR	Newfoundland Familial Colorectal Cancer Registry
NL	Newfoundland and Labrador
NSAID	Nonsteroidal Anti-Inflammatory Drug
OCR	Ontario Cancer Registry
OR	Odds Ratios
OS	Overall Survival
PCA	Principal Component Analysis
PHQ	Personal History Questionnaire
PUFA	Poly Unsaturated fatty acid
RFS	Recommended Food Score
CI	Confidence Interval

Organization of thesis

This thesis is written in a manuscript format. The thesis has four major chapters. Chapter 1 is an overall introduction and overview of the study. Chapter 2 and chapter 3 are two separate manuscripts. The format of the manuscript is according to the Journal in which it has been published or where it is being submitted for publication. Chapter 4 is an overall summary of the study. Some duplication in the background, a methodology was unavoidable.

CHAPTER 1: INTRODUCTION AND OVERVIEW

1.1 Background

Colorectal cancer (CRC) is a leading cause of cancer-related deaths worldwide (1). It is the third most common cancer in men and the second most common amongst women (2). Incidence and mortality rates of CRC vary widely with higher incidence rates in developed nations and lower rates in Asia, Africa, and many Latin American countries (2). CRC is one of the major health problems of increasing significance in Canada, with an estimated 25,100 new cases, and 9,300 deaths in 2015 (3, 4). According to the Canadian Cancer Society, Newfoundland and Labrador (NL), has the highest incidence rate of CRC in Canada at 86 per 100,000 compared to the national average of 62 per 100,000 (4). The high rates of the disease in NL can only be partly explained by a high prevalence of families with a predisposition to hereditary colon cancer (5). Environmental factors play an important role in the risk and the progression of CRC (6-10).

The aetiology of CRC is complex, with both genetic and environmental factors, playing an important role. Genetic predisposition (11), age (12) and gender (13) are non-modifiable risk factors while a lower level of physical activity, western diet, higher alcohol consumption, and smoking and are modifiable factors associated with risk of colorectal cancer (14).

Diet and behavioural factors have an important role in the risk and progression of different chronic diseases including CRC (15). Some studies suggest that diet plays a significant role in the regulation of chronic inflammation (16) by altering blood

inflammatory biomarkers (17). The Inflammatory microenvironment involves the production of cytokines and chemokines leading to tumour initiation, growth, and invasion (18) by activating signalling pathways favouring carcinogenesis (19) and is particularly of significance in CRC and other epithelial cancers (20). Refined and processed foods, red meat and the western pattern diet in general, have been said to have higher inflammatory potential (21) while a prudent diet with higher fruits and vegetables may be anti-inflammatory in action (22).

Epidemiological studies on the role of individual nutrients or food items on disease outcome are often inconclusive, which may in part be due to dietary interactions, multicollinearity (23, 24) and inability to detect small effects (25). Assessing diet pattern have emerged as a possible approach in nutritional epidemiology to explore the combined effects of dietary habits total diet on health (26). Diet patterns not only represent total diet or key factors in the diet (27) and the frequency of its consumption but also reflect an individual's food preferences modulated by the combination of genetic, cultural, social, health, environmental, behavioural and economic determinants (28).

Data-driven and hypothesis-driven are two major approaches that are used in literature to identify diet patterns (29). The former solely reply on inter-correlations among the food items and latter allows the researcher to incorporate their professional knowledge and understanding. Cluster and factor analysis are outcomes independent empirical data-driven/posterior techniques determining dietary behaviour in the study population while index/score-based are hypothesis-driven based on adherence to prior recommendations or guidelines (30). Briefly, cluster analysis (CA) separates individuals into mutually

exclusive, non-overlapping groups based on mean dietary intakes. Food intake common to all individuals contributes less to cluster formation. Optimal clusters are formed by the maximum ratio of variance across the cluster to within the cluster. No gradient is formed hence comparison is done with the reference cluster. Factorial analysis, specifically Principal Component Analysis (PCA), an exploratory approach, reduces a large set of correlated variables to smaller sets of non-correlated variables which capture the majority of dietary variations within the study population. Linear combinations are created and each individual receives a score called factors (31). A higher score represents higher adherence to the particular diet pattern.

Recommended food score (RFS) (32) and alternate Mediterranean diet score (Alt-Med) (33) are commonly used index-based diet patterns for which scoring is based on adherence to a set of dietary guideline or to the Mediterranean diet, respectively. The Dietary Inflammatory Index score (DII) (34) is based on each nutrient's response to six inflammatory biomarkers. The DII allows the dietary intake to classify as pro-inflammatory vs. anti-inflammatory. For such indices, patterns are derived from gradients which are then compared by referring to reference quartiles.

1.2 Rationale of Study

Different diet patterns commonly used in nutrition epidemiological research can be derived using different methods, yet there have been few studies assessing if and how research results may vary in the same population when different methods are used. Comparing across these diet patterns identified by the various methods is recommended to better understand the association between disease and diet (35).

This study aims to assess and compare various different diet patterns while estimating the CRC risk and patient's survival using Newfoundland Colorectal Cancer Cohort. Newfoundland and Labrador have the highest age-adjusted incidence of CRC compared to rest of Canada and unique dietary patterns which makes it an ideal environment in which to study this association.

1.3 Study Objectives

1. To identify various diet patterns by Principal Component Analysis, Cluster Analysis, Recommended Food Score, Alternate Mediterranean Diet Score and Dietary Inflammation Index score

2. To estimate the patient's survival amongst these diet patterns

3. To investigate the association of dietary inflammation on the risk of CRC

4. To compare various diet patterns

1.4 Literature Review

1.4.1 Incidence and mortality of colorectal cancer

Colorectal cancer is the third most common cancer in men and the second most common cancer in women. In 2012, worldwide, it was estimated that 746 000 new cases were diagnosed in men (10% of all incident cancer cases in men) and 614 000 new cases in women (9.2% of all incident cancer cases in women). Amongst them, more than half were in developed countries. There is substantial geographical variation in incidence across the world. The highest age-standardized incidence rates (per 100 000 population) estimated 2012 were in Australia/New Zealand (44.8 and 32.2 cases in men and women, respectively), and the lowest was in western Africa (4.5 and 3.8 cases in men and women, respectively) (36).

Mortality is considerably lower than incidence rate, with an estimated 694 000 CRC deaths in 2012 (8.5% of all cancer deaths that year) due to improved early diagnosis and treatment. More than half of CRC deaths in 2012 were from low-income countries, reflecting poorer survival in these regions. Worldwide, mortality rates vary less than incidence rates. In both sexes, the highest estimated 2012 mortality rates (per 100 000 population) were in central and eastern Europe (20.3 deaths in men and 11.7 in women), and the lowest in western Africa (3.5 deaths in men and 3.0 in women) probably due to poor reporting. (36)

In Canada, 25,100 new cases, and 9,300 deaths were estimated attributed to CRC (3, 4) in 2015. According to the Canadian Cancer Society, Newfoundland and Labrador (NL), has the highest age-standardized incidence rate of CRC in Canada at 86 per 100,000

compared to the national average of 62 per 100,000 (4). Approximately 540 patients are diagnosed with CRC in NL every year.

1.4.2 Pathogenesis of CRC

Colorectal cancer develops through a gradual accumulation of inherited, somatic, and epigenetic changes, leading to the transformation of normal colonic mucosa into invasive cancer cells. Risk of CRC increases with age, by certain high penetrance inherited genetic mutations (familial adenomatous polyposis and hereditary non-polyposis colorectal cancer), several low penetrance mutations (37), and a personal or family history of colorectal neoplasia/ inflammatory bowel diseases (38). Several modifiable factors are also associated with increased risk of CRC including obesity, diet pattern, physical inactivity, smoking, heavy alcohol consumption, type II diabetes, and of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) (39).

1.4.3 Role of Inflammatory cytokines in cancer and chronic diseases

Chronic inflammation is considered to be a hallmark of the causation of cancer and inflammation is mediated by different cytokines (40). Cytokines are broad categories of small proteins that are important in cell signalling. Cytokines include chemokines, interferons, interleukins, lymphokines and tumour necrosis factors. Cytokines are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes, T- lymphocytes and mast cells, as well as endothelial cells, fibroblasts, and various stroma cells (41). Cytokines are involved in leukocyte recruitment and have both synergistic as well as antagonistic interactions with various target cells (42). Although produced by a wide variety of cell types, macrophages and T lymphocytes (T cells) are

the primary producers of cytokines; they have predominantly pro-inflammatory (inflammation-promoting; IL1α, IL1β, IL2, IL6, IL8, IL12, TNFα, IFNγ; or anti-inflammatory (inflammation-suppressive; IL4, IL5, IL10, TGFβ) abilities (43).Several studies have suggested associations between inflammation and cancer development (44). Diet can play an important role in the regulation of chronic inflammation (16) by altering blood inflammatory biomarkers (17)

1.4.3.1 Pro-inflammatory cytokines

C-Reactive proteins (CRP)

CRP is an acute-phase protein found in the blood and synthesized in the liver in response to inflammation. Several prospective studies have demonstrated an association of CRP with chronic diseases/conditions and patient survival (45) though the results are often inconsistent. Pancreatic, oesophageal, and prostate cancers especially have been suggested to be associated with CRP levels (46). Association of CRP with CRC is inconclusive. A meta-analysis of 8-prospective studies showed that increased baseline CRP levels were associated with a modest risk of CRC (47) whereas the other nested case-control study showed a reduction in risk of developing CRC (17). Due to its short half-life, and the fact that different acute and chronic conditions are possibly associated with CRP levels. It is challenging to assess exact amounts of CRP in the blood (46).

TNF-α

TNF- **α** is a signalling protein involved in the systemic inflammation produced by activated macrophages and other cell types such as lymphocytes, NK cells, neutrophils, mast cells, eosinophils and neurons. It promotes the inflammatory response by different

mechanisms. In the liver it stimulates acute-phase proteins, leading to an increase in CRP levels. It also induces insulin resistance by binding to insulin receptor substrate -1 (IRS-1) which impairs insulin signalling. On macrophages, it stimulates phagocytosis and production of other inflammatory cytokines, IL-1 and prostaglandins. It has been suggested that consumption of Dietary fibres, vegetable oil rich in omega 3 can inhibit the synthesis of TNF-α (48, 49).

IL-1B

An IL-1 family is a group of 11 cytokines, which induce a complex network of pro-inflammatory cytokines via the expression of integrins on leukocytes and endothelial cells; they regulate and initiates inflammatory responses (50). Secretion of IL-1 is inhibited by fatty acid Omega-3 (48)

IL-6

Interleukin 6 is secreted by T cells and macrophages to stimulate the immune response, during infection and after trauma, especially with burns or other damaged tissue leading to inflammation. IL-6 together with other cytokines help to activate T cells, increase the number of antibody-producing B-cells and stimulate the release of hormones. However, the prolonged release of IL-6 causes premature death of immune cells ultimately leading to increased risk of tumour growth (51). High-fat diets have been found to be associated with increase in IL-6 (52) whereas Vitamin E, D, Omega-3 fatty acids have been shown to oppose the action of with IL-6 (53, 54)

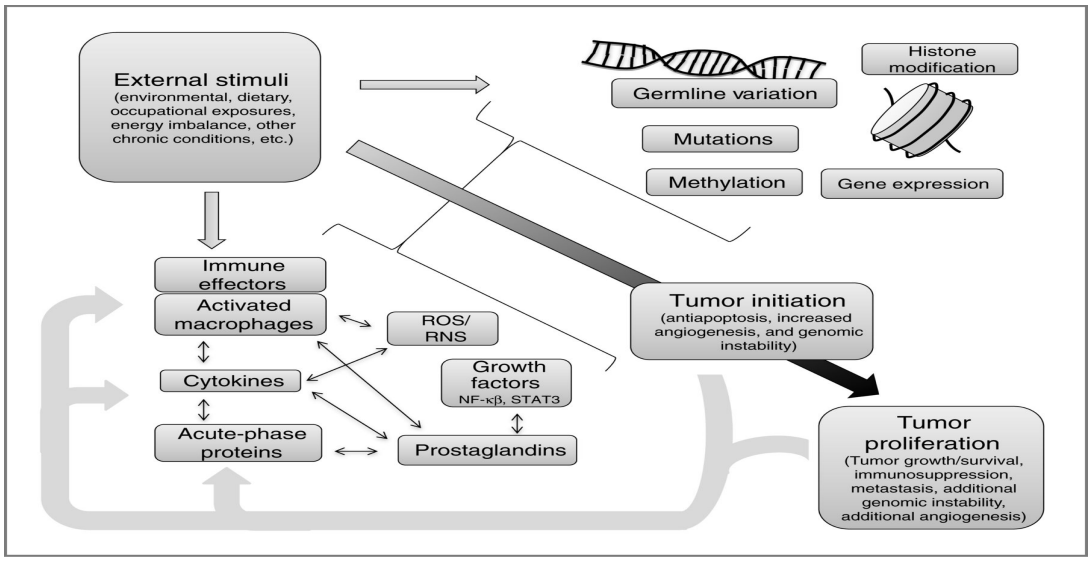

Figure 1 Role of inflammation in the cancer progression (46)

As seen in the figure 1; external stimuli including environmental, dietary, occupational exposures, energy imbalance and any other chronic conditions are responsible for genetic variations and activating the immune effectors. Both of this processes are associated with the tumor initiation by initiating antiapoptosis, increased angiogenesis and genomic instability. Further, this leads to immune suppression, metastasis, additional genomic instability and angiogenesis (46).

1.4.3.2 Anti-inflammatory cytokines

IL-4

Interleukin-4 modulates inflammation and is associated with colorectal adenoma carcinoma progression and metastatic capacity. They are believed to reduce proliferation and arrest cell migration in a dose-response manner (55). Further, it has been suggested

that IL-4 regulates lipid metabolism by inhibiting adipogenesis and promoting lipolysis which in turn may reduce the risk of obesity (56).

IL-10

IL-10 is an anti-inflammatory also known as human cytokine synthesis inhibitory factor (CSIF). IL-10 is a cytokine with multiple, pleiotropic, effects in immune-regulation and inflammation. It down-regulates the expression of Th1 cytokines, MHC class II antigens, and co-stimulatory molecules on macrophages. It also enhances B cell survival, proliferation, and antibody production. IL-10 can block NF-κB activity and is involved in regulation of the JAK-STAT signalling pathway (57).

1.4.4 Factors Associated with the risk of Colorectal Cancer

The aetiology of CRC is complex and multi-factorial (58). Approximately 15% to 20% of all CRCs are familial, and several heritable risk factors and CRC susceptibility genes are involved (59). Majority of CRC cases are sporadic; they arise through cumulative effects of environmental factors and complex interaction between heritable genetic and environmental components (60).

1.4.4.1 Non-modifiable risk factor for CRC

1.4.4.1.1 Family History

The family history of CRC is seen to increase the risk of CRC by two to four times (61). The risk is higher among people whose relatives were diagnosed before 50 years of age (62). A family history of CRC may increase CRC risk by influencing the adenoma growth or enhancing the formation of new lesions. For early diagnosis and treatment, the

American Cancer Society, the US Multi-Society Task Force on CRC, and the American College of Radiology recommends on early screening for individuals with a family history of CRC (63).

Familial adenomatous polyposis (FAP, 1% of all CRC cases) and hereditary non-polyposis CRC(HNPCC, 5%-7% of all CRC cases) are attributed to familial risk (64) and are inherited in an autosomal dominant fashion. FAP is caused by inactivating mutation of a tumour suppressor gene, the adenomatous polyposis coli (APC) gene. Patients affected by FAP usually present with hundreds of adenomatous polyps in the colon, which will inevitability transform to carcinoma if left untreated (65). HNPCC results from mutations in mismatch repair genes, commonly MLH1, MSH2 and MSH6 (65). More than 90% tumours arising in HNPCC patients show microsatellite instability (65).

1.4.4.1.2 Age

Advanced age is one of the most important risk factors for colorectal cancer. According to the American Cancer Society, almost 90% of CRC is diagnosed after the age of 50 years. One of the possible mechanisms is an accumulation of age-associated changes in the biochemical processes that help to control the genes responsible for increased risk of cancer. Advancing age is seen to be linked with increased methylation (66).

1.4.4.1.3 Sex

Risk of CRC is considerably higher in men compared to women (67). Epidemiological studies involving females have shown that increases in female hormones like estrogens

and progestin due to pregnancy or use of exogenous hormones could be associated with a lower risk of CRC (68). However, inconsistencies do exist in these studies (69). Lower androgen levels have been hypothesized to increase the risk of CRC in male (70). Further, differential levels of environmental exposures including smoking, alcohol, and diet patterns intake make men more vulnerable to the development of CRC.

1.4.4.1.4 History of inflammatory disease

History of inflammatory bowel disease (IBD) including ulcerative colitis and Crohn's disease increases the risk of CRC. Dysplasia is a condition where cells in the lining of the colon and rectum change to abnormal cells due to untreated IBD. Although, these are not true cancer cells they are likely to transform to cancerous cells over time hence early screening is recommended.

1.4.4.2 Modifiable Environmental Factors

Different environmental factors have been studied as potential risk factors for CRC both experimentally and epidemiologically. These include dietary factors, physical activity, overweight and obesity, smoking, intake of alcohol, use of inflammatory drugs, and reproductive hormone therapy (HRT) in females.

1.4.4.2.1 Dietary Factors

Diet has been shown to be associated with risk of CRC through a number of possible routes, including physical interaction with the intestinal mucosa (71), alterations in the intestinal microbiota, which are strongly associated with colonic polyp formation (72), or

influence on certain biomarkers in the body. It is estimated that almost 70% of cancer burden could be reduced by alterations in dietary habits (73)

Total Energy and Macronutrients

Total energy intake is seen to be associated with risk of CRC (74-76). Though the underlying biological mechanisms are not fully understood, it is suggested that high energy intake could induce glycaemic overload which increases serum insulin and insulin growth factor-1 (IGF-1), which in turn may promote cell proliferation, inhibit apoptosis, and eventually elevate the risk of colorectal tumorigenesis (77-80).

Fruits and Vegetables

Over 20 case-control (81) and 7 cohort studies (82) have suggested that a high consumption of fruits and vegetables may be associated with a reduction in CRC risk. A protective effect was found for total fruit and vegetable consumption in the 9.6-year follow up of the Swedish Mammography Screening Cohort Study (82). A meta-analysis (83) has suggested that dietary fibre may protect against CRC, although results from prospective cohort studies (84-86) have been negative. The probable reason might be, the protective effect of dietary fibre may require a much longer response latency than the follow-up time frame of the research studies (87).

Dietary fibre

Dietary fibre decreases the risk of CRC by accelerating the transit of gastrointestinal contents, reducing the colonic exposure time to multiple exogenous and endogenous carcinogens (88).Meanwhile, fibres promote the fermentation of food particles in colon

leading to the production of short-chain fatty acids, butyrate a mediator of anti-inflammatory response in the colonic epithelial cells. Phytochemicals are involved in the prevention of oxidative DNA damage, DNA correction mechanism or binding of carcinogens (89).

Red and Processed Meat

"Red meat" is generally defined as flesh from some domesticated animals, which is mainly comprised of red muscle fibres, such as beef, pork, lamb and goat. Red meat is red when it is raw and dark when cooked while white meat is pale in colour before and after cooking. "Processed meat" refers to meats preserved by smoking, curing, or salting, to which nitrites/nitrates or other preservatives are artificially added, such as ham, bacon, and salami (90).

A study reviewed by the 2007 WCRF/AICR panel (90) reported an increased risk for individuals in the highest intake group relative to those in the lowest (based on quartiles), and an apparent dose-response effect has been observed. As well, 12 out of 14 cohort studies (90) have shown a positive association between processed meat intake and CRC risk, with the association being statistically significant in four (91-94). A meta-analysis of five studies showed the relative risk of 1.21 (95% CI 1.04-1.42) per 50 g/day augment of processed meat intake (90). Similarly, a recent meta-analysis of 15 prospective studies, which indicated that a daily increase in red meat consumption by120 gram is associated with a 28% (95%CI: 18%-39%) increase in CRC risk (95).

There are several possible mechanisms that may explain the associations observed between red/processed meat and CRC. First, meat fried or cooked at high-temperatures may contain carcinogenic heterocyclic amines and polycyclic aromatic hydrocarbons (90). Many processed types of meats are also high in salt, nitrites, and nitrates which may subsequently promote the formation of endogenous N-nitroso compounds; these compounds are suspected human carcinogens and have been suggested as significant contributors of CRC development (96, 97), Moreover, high consumption of red meat has been associated with increased iron level, which acts as a possible catalyst to stimulate the production of reactive oxygen species, and hence resulting in DNA damage (98, 99).

Minerals and Vitamins

Several antioxidants such as beta-carotene, riboflavin, folate, and vitamins A, C and D have long been regarded as natural inhibitors that retard cancer initiation or progression (100-104). Since these antioxidants can provide antioxidant and anti-inflammatory effects, it is suggested they protect against CRC. In addition, the vitamins could modulate Treg function and IL-10 production which are important for therapeutic treatment. Vitamin A increases inflammatory response and is involved in tissue damage; moreover, vitamin A is a key modulator of TGF-beta which can suppress several cytokines. Vitamin E, an anti-ageing compound, is associated with a defect of naive T cells and may inhibit some inflammatory compounds such as prostaglandin (105).

In addition, dietary calcium and selenium have consistently been associated with a lower risk of CRC, whereas dietary iron has increased the risk of CRC because of its catalytic

activity on the production of oxygen radicals (101,106). The dosage of these minerals and vitamin plays a vital role in its action.

Milk and dairy products

Epidemiological studies on milk and risk of CRC have mixed results. High calcium content in milk could potentially bind with inflammatory cytokines and thereby reduce cell proliferation and promote cell differentiation (107). On the other hand, the high fat content of milk is likely to increase the risk of CRC by increasing bile acid in the colon (108).

Spices

A growing body of epidemiological and pre-clinical evidence suggests that spices have multiple anticancer properties (109). Capsaicin, a compound present in hot pepper has been seen to activate apoptosis of the cancerous cells (110). Similarly, turmeric (curcumin), cloves (eugenol), ginger (zerumbone), fennel (anethole), kokum (gambogic acid), fenugreek (diosgenin), and black cumin (thymoquinone) appear to have a role in cancer prevention (111). Spices inhibit the synthesis of inflammatory cytokines; they interfere with signalling mechanisms (STAT 3) and gene expressions, work as analogues with the animal sterols (112). Their concentration is vital.

1.4.4.2.2 Cigarette smoking

There are many studies that report a positive association between chronic smoking and elevated risk of CRC (113-120). Risk increases in a dose-dependent manner (113, 114,

116, 117). A meta-analysis (121) suggested that ever smoking was associated with an almost 20% increase in CRC risk compared with never smoking. Risk estimate varied with the location of cancer and as higher for cancer of the rectum than of the colon in current smokers. Tsoi et al. (122) reported that current smokers carried a moderately higher risk of CRC relative to never smokers, and the increased risk of CRC was dose-related to higher levels of daily cigarette consumption/pack-years, and longer years of smoking. Among studies that assessed the effect of smoking cessation on CRC risk, three (120, 123, 124) reported no consistent trend in risk whereas other two (119, 125) reported significantly increased risk with prolonged cessation time.

Different carcinogens are known to be present in cigarette smoke such as polycyclic aromatic hydrocarbons and aromatic amines (126-128) which may reach the bowel mucosa through direct ingestion (129) or through the circulatory system (130), thus exerting growth-promoting effects on cancer cells in the colon/rectum and increasing CRC incidence. Second, tobacco smoking may cause mutation of the GSTM1 gene, resulting in further impaired detoxification of these carcinogens (131). Moreover, smoking may also induce aberrant promoter DNA methylation, thus silencing regulatory genes (e.g., ECAD, p16, MGMT, and DAPK) in tumour initiation and promotion (132).

1.4.4.2.3Physical Activity Levels

Physical inactivity is an established risk factor associated with CRC that is independent of other variables, including obesity (71). Physical activity is believed improve the body's metabolic efficiency and reduces blood pressure and insulin resistance. Most of the epidemiological studies investigating the physical activity and CRC demonstrated a

decreased risk of developing the disease with increased habitual levels of physical activity, except for one early study that reported a positive but non-significant association between physical activity and CRC among men aged <45 years (133). It is estimated that high habitual levels of physical activity could reduce up to 50% of all incidents of CRC (134), and engage in two hours or more of physical activity per week could significantly reduce CRC risk in most people (135).

1.4.5 Factors Associated with Colorectal Cancer Survival

Colorectal cancer survival is mainly associated with stage at diagnosis and histological grade of disease. Generally, earlier the diagnosis, longer the survival. Similarly, lifestyle and behavioural factors affect the survival of CRC patients. Healthier lifestyle before the cancer diagnosis is associated with improved overall survival after CRC diagnosis (136) despite some inconsistencies seen across studies due to limited follow-up duration, sample size and/or methodological issues.

There is enormous variability in CRC survival worldwide. The geographical differences in survival may be in part due to global/regional inequalities in prompt cancer detection and treatment of disease (137). However, survival for CRC at all stages has increased in recent years (137, 138).

1.4.5.1 Non-modifiable factors

Most known factors that influence CRC survival are clinical pathologic features which are unmodifiable, including tumour stage, histological grade, treatments received, and tumour molecular phenotype. Tumour stage and histological grade of CRC are

particularly of importance in the severity of disease and chance of survival. The 5-year survival rate was estimated at over 90% for tumours detected at the localized stage; 70% for regional, and only 10% for people diagnosed with distant metastatic CRC (138). For metastatic CRCs, a systemic treatment appears to largely lengthen the median survival time (139). Further, there is some evidence that associations exist between a tumour molecular features and survival. MSI-H CRCs has been linked to an excellent 5-year survival, while BRAF-mutant tumours have a poor survival (140-142).

1.4.5.2. Modifiable risk factors

1.4.5.2.1 Dietary factors

Diet and nutritional factors are widely believed to act as pro- and antitumor risk modifiers across the entire multi-step process of colorectal tumorigenesis, which includes tumour initiation, promotion and progression. Differences in the rates of CRC by country, and the elevated risks amongst new migrants from a low to the high-risk country, strongly support the importance of environmental factors in CRC risk (143).

Diet has been an important determinant for the survival of colorectal cancer. Several epidemiological studies discussed the role of diet in risk and survival of CRC.

Total Energy and Macronutrients

Epidemiological evidence on the association between intake of total energy and CRC survival remains controversial. Dray et al. (144) analyzed 10-year survival data on 148 patients who received resection of the tumor and concluded that high energy intake, resulting from high intakes of carbohydrate, protein, and lipid, was strongly associated

with better 5-year survival (HRs 0.18) in comparison to the lowest tertiles. Likewise, a study by Slattery et al. (145) showed that the highest quartile of intake for total calories, fat and protein was associated with increased cancer survival. While some recent studies have shown contradicting results. For example, one study (146) showed an adverse impact of a diet high in carbohydrates on disease-free survival, recurrence-free survival, and overall survival of colon cancer patients. Similarly, Sichieri et al. (147) found that total fat intake was positively associated with CRC mortality. The contradictory results are likely to be a consequence of causal or residual confounding factors such as disease stage at diagnosis that had not been adjusted for in earlier studies.

Fruits and Vegetables

Diets higher in fruit and vegetables tend to be associated with a lower risk of CRC mortality (148). The favourable roles of fruit and vegetables on CRC progression may be attributable not only to the antioxidant vitamins or anti-inflammatory potential but also to their fibre content. An ecological analysis of Seven-Country Study (149) showed a strong inverse association between dietary fibre and CRC mortality. Similarly, the Cancer Prevention Study II conducted by researchers from American Cancer Society also observed inverse associations between certain fruits rich in fibre and the risk of fatal CRC (150, 151). As well, Dray et al. (144) found a significant association between fruit, vegetables, and CRC survival.

Red and Processed Meat

Although red and processed meats have been confirmed as a moderate risk factor for CRC (152), minimal research has specifically examined to assess its role in patient's survival. A study by McCullough et al. (153) amongst 2,315 patients with CRC who reported both pre- and post-diagnosis diets in the Cancer Prevention Study II Nutrition Cohort showed that neither pre- nor post-diagnosis red/processed meat consumption was significantly associated with CRC mortality risk; however, individuals with consistently high intakes of red/processed meat before and after diagnosis were 1.79 (95%CI: 1.11-2.89) times more likely to die from CRC than those with consistently low intakes. Similar was the observation in the study by Zell et al. (154). A significant interaction was seen between family history and red/processed meat in McCullough's study. High risk of all-cause mortality was seen in individuals with positive family history.

Overweight and Obesity

Overweight and obesity are linked with the risk of several chronic diseases including the CRC. Results amongst the females are ambiguous. menopausal status, postmenopausal hormone use, and family history of cancer may modify the link between adiposity and colorectal cancer. Similarly, obesity is seen to be strongly related to CRC if an individual has the family history of CRC. Possible mechanisms involve, obese people has chronic low level inflammation, which over the time cause DNA damage that leads to cancer. Adipose tissues produce extra amount of estrogen, which has been associated with the increased risk of cancers. Obese people has high levels of blood insulin which has been

associated with the increased risk of cancer. This has direct effect on the progression of cancer too.

Minerals and Vitamins

Significant associations have been identified between minerals/vitamins and survival from CRC, for example, high premorbid levels of selenium, vitamin B6, retinol, β–carotene, lycopene, total carotene, and pro-vitamin A are seen to be associated with better survival (100, 155-157). However, no consistent trend in risk for death as a result of CRC has been observed for any of the aforementioned nutrients in an ecological survey in 49 Chinese rural counties (148) nor in a study of 16 cohorts of the Seven Countries Study (158). A difference in the findings may be associated with different levels of consumptions.

1.4.5.2.2 Cigarette Smoking

Numerous studies have investigated the role of smoking in CRC survival with conflicting findings. Most studies (159-163), but not all (164-166), have indicated that cigarette smoking is associated with increased risk of CRC mortality and poor survival, specifically for tumors in the rectum than in the colon; however, these associations vary in both direction and magnitude. There have been four main studies that assessed the effect of smoking cessation on the risk of CRC mortality, two of which have reported protective effects of smoking cessation on CRC mortality risk (160, 162). The other two (166, 167)have found no significant association.

A review of 106 observational studies on cigarette smoking in relation to both CRC incidence and mortality by Botteri et al. (121) reported that ever smoking relative to never smoking status was linked with a 1.25 times increased risk. Mortality increased linearly with increasing number of cigarettes smoked per day and prolonged duration of smoking. A study by Liang et al. (168) examined 36 prospective studies and observed almost 40% in RR for CRC mortality in current smokers compared to never smokers. For every additional 20 cigarettes per day, the risk of CRC mortality increased by 40.7%. Some studies have reported non-significant relation in survival rates between smokers and non-smokers with CRC (164-166) which might be attributed to the long induction period of CRC (121), as well as the potential for modulating effects of important prognostic variables (169-171), many of which have not been considered for in those studies.

1.4.5.2.3 Physical Activity Levels

Higher levels of physical activity have been associated with a lower risk of CRC mortality in many epidemiological studies (172-174). In Cancer Prevention Study-II (CPS-II) Nutrition Cohort by Campbell et al. (174) reported protective effects of being physically active both before and after a cancer diagnosis. A 2-year follow-up study in western Australia showed that lower level of physical activity, being overweight/obese, smokers were all associated with poor survival in females but no significant association was seen in the males (175). Similarly, evidence from prospective cohort studies (172), showed that patients who participated in any amount of physical activity before and after diagnosis were found to be at lower risk of CRC-specific mortality compared with patients who did not participate in any physical activity.

1.4.5.2.4 Inflammatory Drugs

Long-term use of Non-steroidal anti-inflammatory drugs (NSAIDs) are associated with the reduced risk of CRC (176). NSAIDs are seen to inhibit cell proliferation rate, alter cell cycle, and induce apoptosis in colon cancer cell lines (177). Results suggest that optimal chemoprevention for CRC requires long-term use of aspirin doses substantially higher than those recommended for prevention of cardiovascular disease (178).

1.4.6 Diet patterns

Epidemiological investigations in the field of nutrition have shifted from the level of individual nutrients to investigations at the level of foods and diet patterns (179) to understand the disease-diet relationship. These combinations of foods, nutrients, or in some cases, foods and nutrients, are often intended to represent the total diet or key factors of the diet. Several reasons are suggested (30); effects of individual nutrients may not be equivalent when foods containing many nutrients are consumed or when foods are consumed as part of a larger diet pattern containing many foods, the magnitude of the effect of individual nutrients is often too small to overcome the noise of confounding and imprecise measurement, whereas the sum effect of many foods may be sufficiently large, correlations among nutrients and among foods are often too high to allow their individual effects to be accurately determined with traditional statistical approaches.

Diet patterns can be identified by various methods which can be broadly classified into data-driven and investigator-driven techniques.

1.4.6.1. Data-driven approaches

Data-driven approaches in diet pattern analyses use mathematics to empirically derive eating behaviour patterns using dietary data collected from FFQs, 24-hour recalls, or diet records. In factor and cluster analyses, a larger set of dietary variables are aggregated to form a smaller set of variables. These methods do not require a prior theory of what patterns are expected, although a thorough understanding of the literature on eating patterns, in conjunction with a theoretical framework for eating behaviour, can be used.

Factor Analysis

The most common factor analysis method used in nutritional epidemiology is principal components analysis, a form of exploratory factor analysis. PCA does not assume an underlying model for the factors and uses matrix algebra to identify the principal components in the data, based on a correlation or covariance matrix of the input variables. The resulting components, or factors, are linear combinations of the observed variables that explain the variance in the data. The factors can be rotated to improve interpretability; orthogonal rotation is commonly used. An output from the PCA includes factor loadings (or scoring coefficients) for each variable, which can be interpreted as correlation coefficients. Factor scores are calculated for each individual by summing the standardized input variables, weighted by their factor loadings. Factor scores are often not correlated with each other. Factors are not mutually exclusive: individuals receive factor scores for each derived factor. Factors are continuous variables that are often categorized into quartiles.

Cluster Analysis

The purpose of CA is to place individuals into groups, or clusters, suggested by the data, not defined a priori, such that objects in a given cluster tend to be similar to each other in some sense, and objects in different clusters tend to be dissimilar. Like factor analysis, CA is also a multivariate method which can be used for characterizing diet patterns. In contrast to factor analysis, CA aggregates individuals into mutually exclusive, non-overlapping, relatively homogenous subgroups (Clusters) with similar diets. Each Individual is positioned in the space and can be classified into distinct clusters or groups on the basis of the frequency of food consumed, a percentage of energy contributed by each food or food group, the average grams of food intake (182), or a combination of dietary and biochemical measures.

By default, the SAS software FASTCLUS procedure uses Euclidean distances, so the cluster centres are based on least squares estimation. This kind of clustering method is often called a k-means model, since the cluster centres are the means of the observations assigned to each cluster when the algorithm is run to complete convergence. Each iteration reduces the least squares criterion until convergence is achieved. Food intake common to all contributes less to cluster formation. Optimal clusters are formed by the maximum ratio of variance across the cluster to within in the cluster. Clusters are categories where the variation of individual foods is not considered after classification. No gradient is formed and the comparison is done across the clusters.

1.4.6.2 Investigator-driven approaches

Score-based approaches are based on dietary recommendations as well as other knowledge about the subject matter. These approaches generally fall into four categories: nutrient adequacy or density scores, variety or diversity scores, food-group patterning scores, and index-based summary scores.

Nutrient Adequacy scores

Nutrient adequacy scores include the nutrient adequacy ratio, defined as average daily intake of a nutrient divided by age- and sex-specific recommended intake of that nutrient, and mean adequacy ratios are defined as the sum of the nutrient adequacy ratio divided by the number of nutrients having a nutrient adequacy ratio. Nutrient adequacy score is developed to evaluate the overall dietary quality of food assistance program. Nutrient density scores were created to evaluate the dietary quality of individual foods in terms of nutrient content in relation to total energy, but do not evaluate total diet pattern (183).

Dietary Variety Scores

Dietary variety scores were started after the introduction of dietary guidelines for Americans in 1980. Variety amongst food groups is defined as the mean number of different food groups consumed daily and variety within the food groups is defined as the mean number of different food subgroups or individual foods within food groups consumed daily.

Dietary variety refers to the mean number of different food groups consumed daily. It considers the number of food groups (i.e. dairy, meat, grain, fruits and vegetables) or food items consumed regularly (184). Both variety amongst the food groups and within a food group explains the variation in mean adequacy ratio scores but are not able to explain the variation in intake of energy, fat, sugar, sodium or cholesterol. First Nation Health and Nutrition Examination Survey have shown that less diverse food groups are associated with increased mortality. Similarly, increased variation within the food groups was positively associated with energy intake. Increased variation within certain food groups e.g. sweets, snacks, condiments and carbohydrates and low variety of fruits and vegetables was positively associated with the body fatness (185).

RFS tallies the foods recommended by current dietary guidelines (32). The RFS is similar to dietary diversity score for recommended foods groups. Currently, dietary guidelines encourage the consumption of fruits, vegetables, and whole grains.

Food Groups Patterning Scores

Food groups patterning scores are based on the five major food groups; fruits, vegetables, grains, dairy and meat. Based on the intake of foods from these groups health outcome is assessed in the study population.

Index based summary scores

The diet quality index is a summary score of the degree to which an individual's diet conforms to specific dietary recommendations. Dietary index approaches is limited by

current knowledge and lack of understanding of the diet-disease relationship. Defining the cut-off points is challenging. Typically, dietary indices are constructed on the basis of prevailing dietary recommendations, some of which may not represent the best available scientific evidence. For example, the healthy eating index is based on adherence to the recommendations of the US Department of Agriculture Food Guide Pyramid.

The Mediterranean diet pattern (MDP), is considered to be one of the healthiest diet patterns. The Mediterranean diet is plant-based, where vegetables, fruits, cereals (preferably with whole grain), legumes, and nuts are consumed in high amount and frequency. MDP also includes moderate consumption of fish and shellfish, white meat, eggs, and dairy products. On the contrary, consumption of red meat, processed meats, and foods rich in sugars and fats should be small in both quantity and frequency(186). The principal source of dietary lipids of the MDP is olive oil and an adequate daily intake of water should be guaranteed. A moderate consumption of wine is recommended. MDP encloses a beneficial fatty acid profile with a high content of MUFA and a higher MUFA/saturated fatty acids (SFA) ratio than non-Mediterranean diets. High consumption of dietary fibre, low glycaemic index and glycaemic load, anti-inflammatory effects, and antioxidant compounds, may act together to produce favourable effects on health status.

The DII is a relatively new dietary index that is based on peer-reviewed research focusing on diet and inflammation and is standardized to world average dietary intake. Chronic inflammation is considered to be the hallmark of the causation and progression of multiple cancers epithelial cancers. DII score is calculated based on the response to six inflammatory biomarkers including IL-1B, IL-6, TNF-α, or CRP (pro-inflammatory) and

IL-4 or IL-10 (anti-inflammatory (34) cytokines. In index based patterns gradients are formed and the comparison is done talking the reference quartile.

Summary of literature review

Colorectal cancer is a leading cause of cancer-related deaths worldwide. Etiology of CRC is complex and multifactorial. Genetic predisposition (11), age (12) and gender (13) are some of the non-modifiable risk factors while the lower level of physical activity, diet pattern, higher alcohol consumption, smoking are the common modifiable factor associated with risk of CRC (14).

The dietary factor is considered to be one of the important determinants of cancer (15). Diet is associated with risk of CRC through either physical interaction with the intestinal mucosa (88) or alterations in the intestinal microbiota, which are strongly associated with colonic polyp formation and with the risk of developing CRC (92). Similarly, diet plays an important role in the regulation of chronic inflammation (16) by altering blood inflammatory biomarkers (17). Chronic inflammation is considered a hallmark of the causation and progression of cancer (40).

Epidemiological studies on the role of individual nutrients or food items on disease outcome are often inconclusive, which may in part be due to dietary interactions, multicollinearity (23, 24) and inability to detect small effects(25). Diet patterns are used commonly in epidemiological research to overcome some of the limitation associated with individual nutrient based studies. Diet patterns not only represent total diet or key factors in the diet (27) and the frequency of its consumption but also reflect an individual's food preferences modulated by the combination of genetic, cultural, social, health, environmental, behavioural and economic determinants (28).

Data-driven and hypothesis-driven are two major approaches that are used in literature to identifying diet patterns (29). The former solely reply on inter-correlations among the food items and latter allows the researcher to incorporate their professional knowledge and understanding. Cluster and factor analysis are outcomes independent empirical data-driven/posterior techniques determining dietary behaviour in the study population while index/score-based are hypothesis-driven based on adherence to prior recommendations or guidelines (30).

This study is designed to assess and compare different diet patterns identified while estimating the CRC patient's survival using the Newfoundland Colorectal Cancer Cohort. Meanwhile, the study investigates the role of diet-mediated inflammation assesses by DII on the risk of CRC. Compared with other parts of Canada NL has largely maintained its traditional diet, a Western-style with the high proportion of red meat and less vegetables and fruits (54). Despite, several studies have suggested the possible connection between single food or nutrients and risk of CRC (54-56) in this population; overall impact of individual's diet has not been adequately assessed. Comparison amongst the diet patterns identified by different techniques will help to better understand the disease-diet interaction.

Co-authorship statement

In the following two manuscripts, Mr Ishor Sharma is listed as first and the order of other co-authors is based on their relative contributions.

Inflammatory diet and risk of colorectal cancer: A population based Case-Control Study in Newfoundland, Canada

Ishor Sharma and Dr Peizhong Peter Wang conceptualized and designed the manuscript. Mr Sharma conducted all the activities including data analysis, writing the manuscript. Nitin Shivappa and Hebert JR developed the original dietary inflammation index score. Dr Wang, Yun Zhu, Jennifer Woodrow, Patrick s Parfery, John R Mclaughlin, Nitin Shivappa, Nitin Shivappa, Hebert JR contributed to the subsequent revision of this article.

Hypothesis and Data-Driven Dietary patterns and Colorectal Cancer Survival: Findings from Newfoundland and Labrador Colorectal Cancer Cohort

All authors have contributed substantially to this work. Ishor Sharma and Dr Peizhong Peter Wang conceptualized and designed the manuscript. Mr. Sharma conducted all the activities including data analysis, writing the manuscript. Dr Wang, Dr Barbara Roebothan Yun Zhu, Jennifer Woodrow, Patrick s Parfery, John R Mclaughlin, contributed to the subsequent revision of this article.

CHAPTER 2: Inflammatory diet and risk of colorectal cancer: A population based Case-Control Study in Newfoundland, Canada

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Abstract

Objective Chronic inflammation is implicated in causing cancer. Diet plays an important role in regulating chronic inflammation by altering circulating levels of inflammatory biomarkers. Effect of single food or nutrient on cancer often is inconclusive; perhaps due to dietary interactions and multicollinearity. The aim of this study was to determine the pre-diagnostic inflammatory potential of overall diet in relation to risk for colorectal cancer (CRC).

Methods: In all, 547 patients with CRC from Newfoundland Familial Colorectal Cancer Registry and 685 controls from the general population were identified. Data on socio-demographic, medical history, lifestyle, and a 169-item food frequency questionnaire were collected retrospectively from both groups. Energy-adjusted Dietary Inflammatory Index (DII) score was calculated and used as both categorical and continuous variables for analysis. Odds ratio (OR) was estimated using multivariable logistic regression after adjusting potential confounders. A linear test for trend was performed using the median value in each quartile.

Results: Overall energy-adjusted mean DII score was −0.81 (range −5.19 to 6.93). Cases (−0.73 ± 1.5) had slightly higher DII scores than controls (−0.89 ± 1.6; $P = 0.04$). After adjusting the potential confounders, a statistically significant association was found between DII score and CRC risk. Using DII as a continuous variable ($[OR]_{continuous}$ 1.10, 95% confidence interval [CI] 1.01–1.20) and categorical variable ($OR_{quartile\ 1\ versus\ 4}$ 1.65, 95% CI 1.13–2.42; $P_{trend} = 0.02$).

Conclusion: Our findings indicate that pro-inflammatory diets are associated with an increased risk for CRC in the Newfoundland population.

Keywords: Colorectal Cancer, Dietary Inflammatory Index, Inflammation, Risk factors

Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths worldwide. It is the third most common cancer in men and second amongst women (188). CRC vary widely with higher incidence rates in developed nations and lower rates in Asian, African, and many Latin American countries. (1) CRC has become one of the major health problems in Canada, with an estimated 26,100 new cases and 9,308 deaths in 2016 (4). According to the Canadian Cancer Society, Newfoundland and Labrador (NL), the most eastern province, has the highest age-standardized incidence rate of CRC in Canada, at 96 per 100,000 compared to the national average of 67 per 100,000 (4). The high rates of the disease in NL can be explained, in part by a high prevalence of families with a predisposition to hereditary colon cancer (5). However, environmental factors that are an important component of CRC risk play a vital role in both the risk and progression of the disease (6-10).

Genetic predisposition (5), age (12), and gender (13) are non-modifiable risk factors while physical inactivity, overweight/obesity, poor diet, excess alcohol consumption, and smoking are modifiable factors associated with risk of CRC (14, 189). Dietary behaviour is considered to be one of the important determinants of cancer (190). Diet plays an important role in the regulation of chronic inflammation (16) by altering levels of circulating inflammatory biomarkers (17). Inflammatory microenvironment involves the production of cytokines and chemokines leading to tumour initiation, growth, and invasion (18) by activating signalling pathways favouring carcinogenesis (19) and is particularly notable in CRC and other epithelial cancers (20).

Refined and processed foods, a typical Western diet pattern including high calorie drinks, soda, canned foods with heavy syrups, cheese, sugary and refined cereals, refined and processed meats, etc., have higher inflammatory potential (21) while a prudent diet pattern with higher intake of fruits and vegetables are anti-inflammatory in nature (22). Despite food, and nutrients including supplements that have been studied independently in relation to the risk and survival of CRC patients, little is known about the net inflammatory potential of overall diet on risk and survival of CRC patients as diet involves complex interactions of nutrients (23, 24). Since foods/nutrients act together (191-194), any assessment of single food or nutrient is likely to be confounded (195, 196). The Dietary Inflammatory Index (DII) assesses the overall dietary inflammatory potential of the diet based on the food/nutrient response to the six inflammatory biomarkers (IL-1β, IL-4, IL-6, IL-10, TNF-α, and C-reactive proteins.)(34). A higher DII score represents greater inflammatory potential. The DII has been validated and used in different studies to assess the effect of dietary inflammation on the risk and survival of chronic diseases and cancers (197, 198).

Compared with other parts of Canada, NL has largely maintained its traditional diet, a Western-style with the high proportion of red meat and the less vegetables and fruits (199). While several studies have suggested the possible connection between food or nutrients and risk of CRC (199-201) in this population, the overall impact of diet has not been assessed. This study aims to determine the pre-diagnostic inflammatory potential of an individual's diet and its association with the risk of CRC in the NL population.

Material and Methods

Study Population. This study utilized data from the previous population-based case-control study from NL (199). CRC cases were recruited using the Newfoundland Colorectal Cancer Registry (NFCCR) which was modelled on the Ontario Familial Colorectal Cancer Registry. Histo-pathologically confirmed cases aged 20-74 years between 1999 and 2003 were included as cases. Incident CRC diagnosis was identified using codes from the International Classification of Diseases 9th revision. Controls were selected from the NL population through random-digit dialling using telephone numbers provided by Bell Aliant (a local telephone company in NL). Controls were age-matched with cases by 5-year strata. Both cases and controls were residents of NL at time of diagnosis or interview. A total of 1,232 participants (547 cases and 685 controls) were included in the study. A detailed description of the selection of cases and controls is described elsewhere (199). Informed consents were obtained from all research participants, and the study was carried out with the approval by the Health Research Ethics Authority, Memorial University of Newfoundland, in accordance with the Declaration of Helsinki.

Exposure variables. Information including personal history, lifestyle, and dietary characteristics was collected using a personal history questionnaire (PHQ) and a food frequency questionnaire (FFQ), which were developed as part of the larger study and were collected retrospectively one year prior to diagnosis or interview. Briefly, the PHQ consisted of 74 questions including the history of bowel screening, medical conditions, use of medications, diet, physical activity, intake of alcohol, tobacco use, socio-

demographic and economic information, and reproductive factors for females. Similarly, dietary intake data were collected using a 169-item FFQ similar to the Ontario FFQ customized to include foods from NL. Nutrient content was calculated using the Canadian Nutrient File, 2005.

Dietary inflammatory index score was calculated as described elsewhere (34). Briefly, an individual's intake of food or nutrients was linked to a global database with mean and standard deviation consumption of up to 45 nutrient parameters. For each subject and each food parameter, a z-score was derived. These scores were converted to a centred percentile score to reduce the effective skewness and multiplied by the respective food parameter effect derived from the literature review and scoring of 1,943 articles. All food parameter-specific DII scores were summed to determine an individual's DII score. The DII score was adjusted for the energy (from macronutrients and alcohol) using the residual method for both male and female separately (202). Ninety-five percentile data for energy was used for the analysis to remove the extreme values from both extremes of the distribution.

A higher DII score represents the greater inflammatory potential of diet. For the current study, 29 food parameters were available and used in computing the DII score. These included carbohydrate, protein, total fat, alcohol, onion, tea, tea (Herbal), pepper, β-carotene, vitamin B-6, Vitamin B-12, caffeine, cholesterol, energy, fibre, folic acid, iron, monounsaturated fatty acid (MUFA), polyunsaturated fatty acid (PUFA), niacin, magnesium, riboflavin, saturated fatty acid, selenium, thiamine, vitamin-E, vitamin-D, vitamin C, and zinc. The Calculated DII scores were analysed categorically and as

continuous variables. Quartiles were based on DII scores in controls, and the respective quartiles are Quartile I (<-2.036), Quartile II (-2.036 to <– 0.88), Quartile III (-0.88 to <0.358), and Quartile IV (≥0.3582).

Adjustment variables. Potential confounding factors include age, sex, body mass index (BMI) (classified as < 25, 25-29.99, ≥30 kg/m^2), physical activity measured (metabolic equivalent hours/week (METs/week classified as <10, 10-49.99, ≥50), medical history including cholesterol level, triglycerides, family history of CRC, polyps, diabetes, history of colon screening, cigarette smoking (classified as: Yes and No; Yes means smoke 1cigarette/day for 3 months or more), and alcohol consumption (classified as: standard drink/week; not at all, <15 standard drink/week, and ≥15 standard drink/week), regular use of medications including non-steroidal anti-inflammatory drugs (NSAIDs), and reported hormone replacement therapy (HRT, females only).

Theory/calculation. Statistical analyses were performed using SAS® statistical software (version 9.4 SAS Institute, Cary, NC, USA). The characteristics of cases and controls were compared by t-test and ANOVA for continuous variables and chi-square test for categorical variables.

Baseline characteristics were examined across the quartiles of DII. Odds ratio and 95% Confidence Interval (OR; 95% CI) were estimated using multivariable logistic regression model adjusting for age in the crude model and age of diagnosis, sex, smoking, history of screening, diabetes, high cholesterol, polyps, and physical activity in the final model. The basis for assessing the role of potential confounding factors included: (1) existing

evidence, (2) biological plausibility, (3) whether the regression coefficient of the primary dependent variable changed by 10% or more after addition of the potentially confounding variable, or (4) whether the covariate entered the model at $P<0.10$. A stepwise selection procedure was used to identify potential confounding factors.

OR for continuous variables were calculated using DII score as a continuous variable. A linear test for trend was performed using the median value in each quartile. All tests of statistical inference employed a two-sided alpha level of 0.05.

Results

Characteristics of Study Subjects

Table 1 Comparison between cases and controls across the baseline characteristics (univariate analysis), Newfoundland and Labrador Case-Control Study, 1999-2003.

Baseline Characteristics	Cases	Controls	P-value
Subjects	547 (44.40)	685 (55.60)	
Age [a]	62.52±9.06	60.53±9.52	<0.001
Energy-adjusted DII	-0.73±1.5	-0.89±1.6	0.04
Sex			
Male	329 (60.15)	405 (59.12)	0.71
Female	218 (39.85)	280 (40.88)	
Co-Morbidity: cholesterol [c] (n=1223)			
High	166(30.51)	252 (37.11)	0.01
Normal	378 (69.49)	427 (62.89)	
Co-Morbidity: Triglyceride [c] (n=1189)			
High	60 (11.41)	68 (10.26)	0.52
Normal	466 (88.59)	595 (89.74)	
Co-Morbidity: Diabetes [c] (n=1223)			
Yes	119 (21.76)	89 (13.17)	0.001
No	428(78.24)	587 (86.83)	
Smoking [c] (n=1232)			
Yes	402 (73.49)	429(62.63)	
No	145 (26.51)	256 (37.37)	0.001
Alcohol: Standard drink/week (n=1186)			
No	213 (41.04)	275 (41.22)	
0-14.99	251 (48.36)	320 (47.97)	0.98
≥15	55 (10.60)	72 (10.79)	
Body Mass Index (kg/m^2) (n=1202)			
<25	150 (28.20)	211 (31.49)	

25-29.99	227 (42.67)	314 (46.86)	0.01
≥30	155 (29.14)	145 (21.64)	
Regular use of NSAIDs (n=1229)			
Yes	181(33.15)	263 (38.51)	
No	365 (66.85)	420 (61.49)	0.05
Use of Hormonal Contraceptives (N=452)			
Yes	98 (44.95)	115 (56.57)	
No	120 (55.05)	119 (43.43)	<0.001
Family History of CRC [c] (n=1232)			
Yes	16 (2.93)	9 (1.31)	0.06
No	531 (97.07)	676 (98.69)	
Physical Activity (Met-hrs./week) (n=1160)			
≤10 (Low)	117 (32.42)	190 (28.19)	
10-49.99 (Med)	167 (30.59)	270 (40.06)	0.002
≥ 50 (High)	202 (37.00)	214 (31.75)	
Total Energy Intake (Kcal/day) [a]			
	2518.3±1066	2305.6±908.4	0.001
Any screening (n=1258)			
Yes	71 (12.97)	146 (21.31)	0.001
No	476 (87.03)	565 (78.69)	
History of Polyp (n=1202)			
Yes	263 (49.07)	85(12.76)	0.001
No	273 (50.93)	581 (87.24)	

[a] Continuous variables were presented as mean ±SD
[b] Categorical variables were presented as numbers (%). Association between baseline variables and subjects were assessed based on Chi-square.
[c] Fisher's Chi-square test
Column total varies due to the missing values

Table 1 shows the characteristic of cases and controls. Mean self-reported blood cholesterol level amongst the controls was higher than the cases. Cases were more likely

to be diabetic, obese, and smokers than controls. Hormonal contraceptive use significantly differed between cases and controls. Total calorie intake for the cases was higher than the controls. Calorie-adjusted mean DII score was -0.81 (SD= ±1.57; Range: -5.19 to 6.93). Cases (-0.73±1.5) had slightly higher DII score than controls (-0.89±1.6) (p=0.04). There was no statistically significant association between sex, triglyceride status, alcohol intake, use of anti-inflammatory drugs, or history of CRC between cases and controls.

Table 2 shows characteristics of the study population across energy-adjusted quartiles of the DII. Younger participants were likely to consume more pro-inflammatory diets. Those who were diagnosed with CRC at younger ages had diets with higher inflammatory potential than those who were diagnosed at older ages. Men and smokers were observed to consume more pro-inflammatory diets. There was no significant association between family history of cancer, history of screening, polyps, use of hormonal contraceptives, use of alcohol, diabetes status, high cholesterol, higher BMI, and self-reported diet.

Table 2: Characteristics of study population across energy-adjusted quartiles of DII (univariate analysis), Newfoundland and Labrador Case-Control Study, 1999-2003.

	Energy Adjusted Dietary Inflammatory Index (Quartiles)				
Characteristics Mean ±SD/%	Quartile 1 (N=308)	Quartile 2 (N=309)	Quartile 3 (N=309)	Quartile 4 (N=306)	P value
Current Age [a]	63.38±8.08	62.11±8.99	60.86±9.4	59.24±10.34	<0.001
Diagnosis age [a] (For cases only)	63.13±7.92	61.64±7.96	60.09±9.02	57.23±9.95	0.001

Sex					
Male	149 (48.38)	174 (56.31)	203 (65.70)	208 (67.97)	0.001
Female	159 (51.62)	135 (43.69)	106 (34.30)	98 (32.03)	
Diagnosis Age/ Interview (n=1231)					
18-49	15 (4.87)	31 (10.03)	38 (12.30)	60 (19.67)	
50-59	87 (28.25)	94 (30.42)	101 (32.69)	88 (28.85)	0.001
60+	206 (66.88)	184 (59.55)	170 (55.01)	157 (51.48)	
Body Mass Index (kg/m^2) (n=1202)					
<25	102 (33.44)	90 (30.00)	83 (27.48)	86 (29.15)	
25-29.99	143 (46.89)	133 (44.33)	139 (46.03)	126 (42.71)	0.273
≥30	60 (19.67)	77 (25.67)	80 (26.49)	83 (28.14)	
Level of Physical activity Mets/week (n=1215)					
<10 (Low)	64 (22.62)	98 (31.92)	97 (31.80)	103 (33.99)	0.0018
10-49.99 (Med)	136 (44.59)	102 (33.23)	91 (29.84)	108 (35.64)	
≥50 (High)	100 (32.79)	107 (34.85)	117 (38.36)	92 (30.36)	
Smoking (n=1232)					
Yes	187 (60.71)	199 (64.40)	214 (69.26)	231 (75.49)	0.007
No	121 (39.29)	110 (35.60)	95 (30.74)	75 (24.51)	
Alcohol (Standard drink/week) (n=1186)					
No	136 (44.74)	121 (41.72)	122 (40.40)	109 (37.59)	
0-14.99	146 (48.03)	140 (48.28)	146 (48.34)	139 (47.93)	0.15
≥ 15	22 (7.24)	29 (10.00)	34 (11.26)	42 (14.48)	
Co-Morbidity: Diabetes (n=1223)					
Yes	62 (20.33)	55 (18.03)	53 (17.15)	38 (12.50)	0.07
No	243 (79.67)	250 (81.97)	256 (82.85)	266 (87.50)	
Co-Morbidity: High Cholesterol Status (n=1223)					
Yes	116 (37.78)	100 (33.00)	108 (35.18)	94 (30.72)	0.29
No	191 (62.21)	203 (67.00)	199 (64.82)	212 (69.28)	
Co-Morbidity: High Triglyceride (n=1189)					
Yes	40 (13.56)	38 (12.71)	26 (8.72)	24 (8.08)	0.06
No	255 (86.44)	261 (87.29)	272 (91.28)	273 (91.92)	

Co-Morbidity: History of Polyp (n=1202)					
Yes	88 (28.66)	91 (30.43)	84 (28.47)	85 (28.24)	
No	219 (71.33)	208 (69.57)	211 (71.53)	216 (71.76)	0.93
Use of Non-steroidal Anti-Inflammatory Drugs (n=1229)					
Yes	124 (40.26)	109 (35.39)	120 (38.83)	91 (29.93)	0.03
No	184 (59.74)	199 (64.61)	189 (61.17)	213 (70.07)	
Family History of CRC (n=1232)					
Yes	10 (3.25)	4 (1.29)	2 (0.65)	9 (2.94)	0.06
No	298 (96.75)	305 (98.71)	307 (99.35)	297 (97.06)	
Screening (n=1232)					
Yes	63 (20.45)	64 (20.71)	45 (14.56)	45 (14.71)	0.05
No	245 (79.55)	245 (79.29)	264 (85.44)	261 (85.29)	

[a] Continuous variables were presented as mean ± SD.
Test/ANOVA and Chi-square tests are used for the continuous and categorical variables, respectively

Table 3 OR of CRC for energy-adjusted DII amongst cases and controls (multivariable-adjusted analysis), Newfoundland and Labrador Case-Control Study, 1999-2003.

	Quartile1 (N=308)	Quartile 2 (N=309)	Quartile 3 (N=309)	Quartile 4 (N=306)	P trend	OR[a]
Case	117	150	135	145		
Control	191	159	174	161		
Crude OR	1[#]	1.54 (1.18-2.12)	1.267 (0.91-1.74)	1.46 (1.05-2.01)	0.040	1.05 (0.98-1.14)
Age-adjusted OR	1[#]	1.59 (1.15-2.20)	1.35 (0.98-1.87)	1.64 (1.18-2.27)	0.011	1.09 (1.01-1.17)
Multivariate OR**	1[#]	1.61 (1.1-2.34)	1.29 0.89-1.89)	1.65 (1.13-2.42)	0.03	1.10 (1.01-1.20)

[#] Reference category
** Adjusted for age, sex, diabetes, cholesterol, smoking, alcohol intake, physical activity, screening history, and use of inflammatory drugs
[a] Odds Ratio (OR) for the continuous variable
Figures in parenthesis shows the 95 % confidence intervals

Crude and adjusted OR is shown in Table 3. In crude analysis, there was a significant association between DII quartiles and risk of colorectal cancer (OR $_{\text{quartile 1 vs. 4}}$ 1.46 95% CI 1.05-2.01; *p*- trend =0.045). The relation was not significant while using DII as a continuous variable (OR $_{\text{continuous}}$ 1.05, 95% CI 0.984, 1.135). In age-adjusted model, a positive association was seen between DII and CRC (OR $_{\text{continuous}}$ 1.09, 95% CI 1.01, 1.17) and (OR $_{\text{quartile 1 vs. 4}}$ 1.64, 95% CI 1.18, 2.27; *p*.trend =0.01). Similarly, in the multivariable model after adjusting for the potential confounders, significant associations

were observed between DII score and risk of CRC (OR $_{\text{continuous}}$ 1.10, 95% CI 1.01, 1.20) and (OR $_{\text{quartile 1vs 4,}}$ 1.65, 95% CI 1.13 - 2.42), (*p*-trend = 0.03).

Discussion

In this study, we compared the DII score in cases and controls as both a categorical and a continuous variable. The results showed increased CRC risk with a pro-inflammatory diet.

Previous studies on the same NL population have reported the increased risk of CRC with pickled red meat (199), total energy intake (36), and an inverse association with vitamin D and calcium (203). Similarly, other epidemiological studies have revealed an association between CRC and higher dietary cholesterol and total saturated fat (204). In contrast, increased consumption of total fibre (205), PUFA (206), and micronutrients and spices (turmeric, cloves, ginger, fennel, kokum, fenugreek, and black cumin) are seen to be protective against CRC (112). However, these study findings are limited to these foods, and nutrients are consumed together with other food items and nutrients, and thus the dietary interactions may confound the associations (195, 196).

A normal human diet consists of foods with both pro-inflammatory and anti-inflammatory properties (207). The DII score measures the overall functional aspects of food and nutrients on the basis of inflammatory potential (34). Epidemiological studies have shown the positive association between DII score and circulating levels of inflammatory markers (208), suggesting the effectiveness of the use of DII in assessing

the risk of chronic diseases including cancers. One of the possible mechanisms for the diet causing CRC is through the increasing level of (C- Reactive Proteins) CRP and adhesions molecules (209). These molecules lead to an increase in insulin resistance (210), which is associated with CRC. Similarly, inflammatory microenvironment involves the production of cytokines (interleukins, tumour necrosis factors, etc.) and chemokines leading to tumour initiation, growth, and invasion (18) by activating signalling pathways favouring carcinogenesis (19).

Findings from this study are in line with previous studies. Mean DII in the current study was -0.81 (SD±1.57), which is similar to the levels observed in the Iowa Women's Health Study; i.e., -0.87 (SD ±2.02) (211). The current study showed an almost 60% increase in CRC risk comparing the highest DII quartile to reference quartile after adjusting for potential confounders. This increase is much higher than what was observed in either the Iowa Women's Health Study (20%) (211) or the Women's Health Initiative (35%) (212). Higher risk in this population might be due to its unique diet pattern, which is characterized by high consumption of pickled and red meats and low intake of fruits and vegetables(199). Similarly, higher risk associated with more of inflammatory diet was seen for CRC in the Bellvitge Colorectal Cancer Case-Control Study (213). The DII has been associated with the risk of other cancers. For example, the risk of prostate cancer is seen to be associated with a higher DII score in a Jamaican study (214). In an Italian Case-Control study, the DII was associated with an increased risk of laryngeal cancer (215).

No other variable (age groups, body mass index, history of polyps, co-morbidities including diabetes, high cholesterol, sex, physical activity, location by the anatomical sites, or use of anti-inflammatory drugs) was found to significantly modify the association between DII score and risk of the CRC (all P -for interaction >0.05). Statistically, significant effect modification has been inconsistent across studies (212, 216) suggesting the complexity of environmental factors with the risk of CRC. An earlier study in NL suggested that the higher incidence of CRC attributed to genetic factors, which might be distributed more or less equally in both cases and controls; NL is seen to have a unique founder population effect (5).

This study has some limitations. Recall bias may distort results because the dietary recall was directed towards intake one year prior to diagnosis or the date of interview. However, there is evidence to suggest that diet pattern tends to remain relatively stable over time (217). The dietary supplement can also modify the inflammatory potential of diet. However, in this study dietary supplementation was not considered which might have underestimated the intake of some nutrients. The results from the current study are limited to a population of primarily European origin as they were more than 95% of the study population. It should be noted that polymorphisms of inflammatory genes may affect levels of circulating inflammatory biomarkers and, therefore, influences the association with CRC (218). Similarly, while classifying the study population based on the BMI all individuals with BMI below 25kg/m^2 were included in the same group as the percentage of individual below 18.5kg/m^2 was minimal.

Conclusion

In conclusion, pro-inflammatory diets appear to be associated with increased risk of CRC in NL population suggesting dietary-mediated inflammation plays an important role in colon carcinogenesis.

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Conflict of Interest

This research was supported by Newfoundland and Labrador Healthy Aging Research Program (NL-HARP) grant and Translational and Personalized Medicine Initiative (TPMI) grant. Dr Hebert and his team from the North Carolina University was supported by United States National Institute of Diabetes, Digestive and Kidney Diseases (grant number R44 DK103377). JRH owns a controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the DII from the University of South Carolina to develop computer and smartphone applications for patient counselling and dietary intervention in clinical settings. The other authors have no conflicts of interest to declare.

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CHAPTER 3: Hypothesis and Data-Driven Dietary Patterns and Colorectal Cancer Survival: Findings from Newfoundland and Labrador Familial Colorectal Cancer Cohort

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Abstract

Background Diet patterns are used commonly in epidemiological research, yet there have been few studies assessing if and how research results may vary across diet patterns. This study aimed to estimate survival outcomes using different diet patterns and compare amongst the diet patterns in the Newfoundland and Labrador Colorectal Cancer cohort.

Methods Data-driven diet pattern (Cluster Analysis (CA), Principal Component Analysis (PCA)) and hypothesis-driven pattern (Alternate Mediterranean Diet (Alt-Med), Recommended Food (RFS), Dietary Inflammatory Index (DII) scores) were identified using 169-item food frequency questionnaire. A total of 532 cases diagnosed between 1999 and 2003 were followed until 2010. Overall survival (OS) and Disease-Free Survival (DFS) time were calculated. Comparisons were made with adjusted Cox proportional Hazards Ratios (HRs), correlation coefficients and the distributions of individuals in defined clusters by quartiles of factor and index scores.

Results A total of 170 cases died from any cause and 29 had a cancer recurrence/metastasis during follow-up. Processed meats as classified by PCA (HR 1.82; 95% confidence interval (CI) 1.07-3.09), clusters characterized by meat and dairy products (HR 2.19; 95% CI 1.03-4.67) and total grains, sugar, soft drinks (HR 1.95; 95% CI 1.13-3.37) were associated with poor DFS. Poor adherence to Alt-Med was associated with higher risk of all-cause mortality (HR 1.62; 95% CI 1.04-2.56). Prudent vegetable, high sugar pattern, RFS and DII had no significant association with both OS and DFS.

Conclusion Survival outcome estimation varied across the diet pattern which is attributed to the differences in the foundation of each pattern.

Keywords: Colorectal Cancer - Diet patterns - Factor analysis - Cluster analysis - Index analysis

Background

Diet and behavioural factors have crucial roles in the risk and progression of several chronic diseases including colorectal cancer (CRC) (15). Epidemiological studies on the role of a single nutrient or food items on disease outcome are often inconclusive, which may in part be due to dietary interactions, multicollinearity (23, 24) and/or inability to detect small effects (25). Diet patterns are advantageous in nutritional epidemiology to explore the combined effects of total diet on health and to some extent overcome these limitations (26). Diet patterns not only represent total diet or key factors of diet (27) and the frequency by which foods are habitually consumed, but also reflect an individual's food preferences modulated by a combination of genetic, cultural, social, health, environmental, behavioural and economic determinants (28).

Data-driven and hypothesis-driven are two major approaches to identify diet patterns (29). Cluster and factor analysis are outcome independent empirical data-driven techniques determining dietary behaviour in the study population while index/score-based are hypothesis-driven based on adherence to prior recommendations or guidelines (30). Studies on how outcome estimation may vary across these different patterns are limited and comparing across the patterns is recommended to better understand disease diet association (35). However, such studies are limited. This study aimed to investigate and compare the relation between various pre-diagnostic diet patterns and risk of mortality in CRC patients using the Newfoundland and Labrador Familial Colorectal Cancer cohort.

Briefly, cluster analysis (CA) divides individuals into mutually exclusive, non-overlapping groups based on mean dietary intakes (gm) (182). Food intake common to all contributes less to cluster formation. Optimal clusters formed by the maximum ratio of variance across the cluster to within the cluster. No gradient is formed hence comparison is done with the reference cluster. Factorial analysis, specifically Principal Component Analysis (PCA), an exploratory approach, reduces a large set of correlated variables to smaller sets of non-correlated variables, which captures the majority of dietary variations within the study population. Linear combinations are created and each individual receives a score called factors (31). A higher score represents higher adherence to the particular diet pattern.

Recommended food score (RFS) (32) and alternate Mediterranean diet score (Alt-Med) (33) are commonly used index-based diet patterns for which scoring is based on adherence to US dietary guidelines and the Mediterranean diet, respectively. The Dietary Inflammatory Index score (DII) (34) is based on each nutrient response to six inflammatory biomarkers which leads to dietary intake being classified as pro-inflammatory vs. anti-inflammatory. For such indexes, patterns were derived from gradients, which are then compared by referring to reference quartiles.

Methods and Materials

Study population

This study used data from the Newfoundland Familial Colorectal Cancer Registry (NFCCR). Five hundred and thirty-two pathologically confirmed CRC patients diagnosed

between 1999 and 2003 and aged 20-75 years were included in the study. A detailed description of the study population is published elsewhere (219). Briefly, CRC cases followed from the date of diagnosis until April 30th, 2010. Overall survival (OS; the time between the dates of diagnosis to the date of death from all causes until end of follow up period) and Disease-free survival (DFS; the time between the dates of diagnosis to the date of death, recurrence, or metastasis (whichever came first) was calculated.

Study outcomes were obtained using follow-up questionnaires, local newspapers (e.g., death notices), death certificates, autopsy, pathology, radiology, surgical reports, as well as physician's notes. Additional data gathered from the Dr H. Bliss Murphy Cancer Care Foundation and Statistics Canada (220). As cause-specific death was not available for all deceased participants, all-cause mortality used for analysis. Patients without the event of interest were censored at the date of the last contact.

Data collection tools

Participants completing the consent were asked to complete validated food frequency questionnaire (FFQ) (221), personal history questionnaire (PHQ) and some further questions pertaining to family history and medical history. Briefly, the PHQ consisted of 74 questions including the history of bowel screening, medical conditions, use of medications, physical activity, intake of alcohol, tobacco use, socio-demographic information, and reproductive factors for females. Similarly, dietary intake data were collected using a 169-item FFQ retrospectively a year before the diagnosis. Nutrient content calculated using the Canadian Nutrient File, 2005.

MSI (Microsatellite instability) and BRAF have been associated with cancer prognosis and survival (222, 223). P V600E BRAF mutation and MSI for the tumour DNA have been determined in a previous study using standard protocol(224). MSI status was defined as MS high if 30% or more of the markers were unstable and MS-stable/MS-low if less than 30% showed instability (225).

Identifying diet patterns

For CA, 169 food items were classified into 39 different food groups depending on the ways they are taken (cooked, raw, drinks, etc.) and nutrient profile. Food groupings are attached in Appendix 1. Clusters were identified by using K-means non-hierarchical method, an iterative technique which groups data into k clusters in such a way as to maximize the R2 (R2 = 1 − W/T), where W is the sum of squared Euclidean distances between each data point and its within-cluster mean, and T is the sum of squared distances between each data point and the overall mean. FASTCLUS procedure in SAS was applied. Clusters with less than 5 participants were temporarily removed while forming the stable cluster. A detailed description of cluster formation is described elsewhere (225). Overall, four stable clusters were identified. Characteristics of clusters are given in appendix 2.

Three patterns were identified using the PCA. Briefly, exploratory principal component factor analysis was conducted using the same 39 predefined food groups. A varimax rotation (orthogonal) was applied to identify uncorrelated food groups. Factor Eigen value greater than 1.15, the scree plot and proportion of variance explained were used to

identify the number of factors. Patterns were labelled based on factor loading ≥ 0.5. The factor score of each participant was obtained by summing the intake of each food group multiplied by optimal weights and divided into quartiles. A higher factor score represents greater adherence to that particular diet pattern. Factor loading and explained variances for three major diet patterns are shown in appendix 3.

The RFS method developed by Kent, et.al (32) is based on fruits, vegetables, whole grains, lean meats or meat alternatives, and low-fat dairy products. Each individual is given 1 point for each recommended food consumed at least weekly. Based on FFQ, the maximum score is 47. Total RFS score varies with the number of food items in the FFQ (227). A higher score represents better adherence to RFS. Details are attached in Appendix 4.

The Alt-Med score is based on the Mediterranean diet scale (228); scoring is based on 9 food groups. If the intake (servings/day) of a particular food group is greater than the median, then it is scored one (versus zero). For red and processed meat, reverse scoring is done. For alcohol, if intake is between 5-25 g/d, then it is scored as 1 (versus zero). The maximum Alt-Med score is 9 with a higher score representing better adherence to the Alt-Med diet. Details of the food groups are attached in Appendix 5.

Detailed descriptions of the DII score are provided elsewhere (34, 187). Briefly, a total of 29 nutrient parameters were scored based on their inflammatory response to 6 inflammatory biomarkers; IL-1β, IL-4, IL-6, IL-10, CRP and tumour necrosis factor (TNF-α). These included carbohydrate, protein, total fat, alcohol, onion, tea, tea (herbal),

pepper, β-carotene, Vitamin B-6, Vitamin B-12, caffeine, cholesterol, energy, fibre, folic acid, iron, monounsaturated fatty acid (MUFA), polyunsaturated fatty acid (PUFA), niacin, magnesium, riboflavin, saturated fatty acid, selenium, thiamine, Vitamin-E, Vitamin-D, Vitamin-C and zinc. A higher score represents the higher inflammatory potential of the diet. All index-based scores are categorized into quartiles for analysis.

Statistical analysis

Adjusted hazards ratios were estimated using Cox proportional hazard analysis using SAS version 9.4 (SAS Institute, Inc. Cary). Comparisons across patterns were made with adjusted HRs, correlation coefficients and distributions of individuals in clusters by quartile of factor and index scores. Potential confounding factors include age; sex; body mass index (BMI) (classified as < 25, 25-29.99, ≥30 kg/m2); physical activity (metabolic equivalent hours/week, METs/week, classified as <10, 10-50, ≥50); medical history including cholesterol level; triglycerides; family history of CRC; polyps; diabetes; history of screening; smoking (classified: Yes and No; Yes means smoke at least 1 cigarette/day for 3 months or more); alcohol consumption (classified: standard drink/week; not at all, <15 and ≥15); and regular medication usage including non-steroidal anti-inflammatory drugs (NSAID) and reported hormone replacement therapy (HRT, females only). Energy adjustment was done using the residual method wherever applicable (229).

The basis for assessing potential confounding factors included: existing evidence, biological plausibility, whether the regression coefficient of the primary variable of

interest changed by 10% or more after addition of the potentially confounding variable for every covariate entered model at P<0.10. A stepwise selection procedure used to identify potential confounding factors.

Results

Characteristics of study population

Mean age of participants and mean age at diagnosis was 62.53±9.06 years and 60.42±9.02 years, respectively. A total of 170 cases died from all causes and 29 had a cancer recurrence or metastasis at the end of the follow-up. Median Overall survival (OS) time was 6.42 years (Range: 1.34-10.88 years). Almost 68% of the participants were censored for OS and 62.6% for DFS during analysis.

Table 4 Characteristics of study participants with their overall survival status (Univariate); Newfoundland and Labrador Familial Colorectal Cancer Cohort (1999-2003)

Characteristic	No. of patients*	No. of deaths (%)	P log-rank
Age at diagnosis			
≤60	231	62 (26.83)	
>60	301	108 (35.88)	0.04
Sex			
Female	211	57 (27.02)	
Male	321	113 (35.20)	0.02
Family history			
Yes	16	6 (37.5)	
No	516	164 (31.78)	0.61

Reported screening procedure			
Yes	68	15 (22.05)	
No	464	155 (33.4)	0.08
Stage at diagnosis			
I/II	311	74 (23.79)	
III/IV	221	96 (43.43)	<0.001
Diabetes History			
Yes	115	42 (36.52)	0.22
No	417	128 (30.69)	
History of High Cholesterol			
Yes	153	44 (28.75)	
No	349	117 (33.52)	0.44
Tumour location			
Colon	349	105 (30.09)	
Rectum	183	65 (35.51)	0.25
Smoke			
Never	139	34 (24.44)	
Yes	393	136 (34.60)	0.07
Physical Activity (Met-hrs/week)			
Low (<10)	175	52 (29.71)	
Median (10-50)	163	56 (34.35)	0.27
High (50+)	193	62 (32.12)	
MSI status			
MSI-L	440	154 (35.0)	
MSI-H	61	6 (9.83)	<0.002
Reported chemo Therapy			
Yes	108	42 (38.88)	
No	421	128 (30.40)	0.06

MSI, Microsatellite instability; MSI-L, Microsatellite instability low; MSI-H Microsatellite instability High * Column total varies due to missing values.

Table 4 presents the characteristics of the study population with the log-rank test. In the univariate test, there is a significant difference in the OS across the age groups, gender, diagnosis stage and microsatellite instability status. A family history of CRC, reported screening status, history of co-morbidity including diabetes, higher blood cholesterol level, the location of a tumour, smoking status, physical activity and reported chemotherapy had no significant association with the survival.

Diet patterns and survival outcome estimation

Table 5 Diet patterns and Colorectal Cancer Survival (Multivariable adjusted analysis); Newfoundland and Labrador Familial Colorectal Cancer Cohort (1999-2003)

Diet Pattern Identified by	**Disease-free Survival**		**Overall Survival**	
	HR* (95% CI)	P-trend	HR (95% CI)	p-trend
Factor Analysis				
Processed Meat pattern*	**1.82 (1.07 -3.09)**	0.09	1.53 (0.85-2.27)	0.25
Prudent Vegetable Pattern*	1.12 (0.69-1.84)	0.62	1.03 (0.61-1.75)	0.90
High-sugar Pattern*	1.02 (0.62-1.69)	0.89	1.27 (0.72-2.23)	0.62
Cluster Analysis				
Fruit and Veg, Whole Grain, Fish, wine (Cluster I)	1#		1#	
Meat, dairy products(Cluster II),	**2.19 (1.03-4.67)**		2.04 (0.96-4.35)	
Refined grains, sugar soft Drinks (Cluster III)	**1.95 (1.13-3.37)**		**2.05 (1.18-3.57)**	
Many foods (Cluster IV)	1.55 (0.92-2.61)		1.50 (0.9-2.56)	
Index Based				
DII*	0.89 (0.56-1.42)	0.46	0.78 (0.47-1.25)	0.33
Alt. Mediterranean Diet Score**	1.44 (0.92-2.25)	0.08	**1.62 (1.04-2.56)**	0.03
Recommended Food Score**	1.51(0.92-2.48)	0.06	1.54(0.92-2.56)	0.045

*Hazards Ratio while comparing with the highest quartile to the lowest (reference quartile)
** Hazards Ratio while comparing with the lowest quartile to highest (reference quartile)
# Reference group
HR ratios Adjusted for energy, stage of cancer, sex, age, marital status, tumour location, screening history, intake of alcohol, radiation and chemotherapy status, Microsatellite instability status wherever applicable
Events are defined as all-cause deaths for overall survival and death/recurrence/metastasis (which occurred earliest) for disease-free survival;

Table 5 shows the estimated adjusted hazards ratio corresponding to different diet patterns with 95% confidence interval. Survival estimation varies with the diet pattern. Four different clusters were identified. When compared with the reference cluster characterized by higher intake of fruits, vegetables, whole grains and wine (Cluster I), the cluster characterized by high intake of meat and dairy products (Cluster II) had significant worse DFS outcome (HR 2.19, 95% 1.03-4.67). The cluster characterized by a higher intake of refined grains, and sugar/soft drinks (Cluster III) had both poor DFS (HR 1.95, 95% 1.13-3.37)and OS (HR 2.05, 95% 1.18-3.57) outcomes. The cluster characterized by the many food groups (Cluster IV) had no significant relation with either OS or DFS. This cluster that was based on many foods (cluster IV). No any specific distinguishing or dominating food item could be identified.

Three diet patterns were identified using PCA: processed meat pattern, prudent vegetable pattern and high sugar pattern. Though the overall trend was not significant (p=0.09), the highest quartile of processed meat pattern significantly worse DFS (HR 1.82, 95% CI 1.07-3.09), however, there was no significant association with OS. Neither the prudent vegetable pattern nor the high sugar pattern showed a significant outcome with both DFS and OS.

While using index-based patterns, DII and RFS showed no significant association with either OS or DFS outcomes. The lowest quartile of the Alt-Med score was significantly

associated with the worse OS outcome (HR 1.62, 95% 1.04-2.56) but had no significant association with the DFS outcome.

Comparison amongst the diet patterns

Table 6 Spearman's Correlation coefficients amongst the index-based scores obtained from FFQ; Newfoundland and Labrador Familial Colorectal Cancer Cohort (1999-2003)

	RFS	**DII**	**AltMED Score**
RFS	1	-0.61**	0.60**
		<0.001	<0.001
DII		1	-0.61**
			<0.001
Alt-Med			1

DII, Dietary inflammatory Index; Alt-Med Diet, Alternate Mediterranean diet; RFS, Recommended Food Score ** Significant at 0.05.

Correlation coefficients amongst the index-based scores are described in table 6. Correlations were high and significant because of the similarity in the food items in scoring. A significant positive correlation was observed between RFS and the Alt-Med score (0.60; p=0.001). Significant negative correlations were found between the DII score and the Alt-Med (-0.601; p= 0.001) and RFS (-0.602; p=0.001) scores.

Table 7 Percentage of individuals in each cluster in highest/lowest quartile of factor/index score; Newfoundland and Labrador Familial Colorectal Cancer Cohort (1999-2003)

	Cluster I	**Cluster II**	**Cluster III**	**Cluster IV**
Characteristics of Cluster	Fruits and Veg, whole grain, fish, wine	Meat, Dairy products, mixed dishes	Sugar/ drinks, total cereals and grains (refined included)	Many foods
Principle Component Analysis **				
Processed Meat pattern	15.29	**91.89**	38.38	16.21
Prudent vegetable pattern	**58.60**	24.32	6.06	11.46
High Sugar pattern	17.20	10.81	16.16	**35.18**
Index based				
DII *	**64.97**	13.51	10.1	7.91
AltMed Diet **	**36.31**	8.11	6.06	9.88
RFS **	**57.32**	35.14	13.13	11.86

DII, Dietary inflammatory Index; AltMed Diet, Alternate Mediterranean diet; RFS, Recommended Food Score ** Highest Quartile (reference) * Lowest Quartile (reference)

Table 7 examines the percentage of individuals in the highest quartile of factor and index score in different cluster describing some level of similarity in the foundation of scale. Almost 92% of individuals from the processed meat pattern were in Cluster II characterized by meat and dairy products. Approx. 59% of individuals from highest quartile of the prudent vegetable pattern were in Cluster I characterized by fruits and

vegetables, whole grain, fish and wine. Around 35% of individuals in the highest quartile of high sugar pattern were in the many foods group. In all three index-based patterns, lowest quartile of DII and highest quartile of Alt-Med and RFS showed the higher proportion of individuals from Cluster I characterized by fruits and vegetables, whole grain, fish and wine (64.97%, 36.31% and 57.32% respectively).

Discussions

Both data-driven and hypothesis-driven diet patterns were determined and relation with colorectal cancer patient's survival was estimated. The hypothesis-driven pattern showed how study population is adherent to dietary recommendation while data-driven pattern explains how whole population dietary practice can be classified into different categories. As each diet pattern was designed to answer the different question, the discrepancy in the outcome estimation was expected despite some level of similarity in the foundation of diet patterns.

In current study as identified by CA, the meat and dairy product cluster was associated with poor DFS while the refined grains, sugar, soft drinks cluster were associated with both poor DFS and OS. A processed meat pattern as identified by PCA was associated with poor DFS. Low adherence to the Mediterranean diet was associated with the poor OS. RFS and DII had no significant association with the survival outcomes. The magnitude of estimated HR also varied accordingly.

Epidemiological studies reveal inconsistent results while assessing the relation between diet patterns and disease outcome in the same population, which is in line with the current

study. A study by Reedy J; et.al (35) showed that among males diet patterns and clusters characterized by fruits, vegetables, lower fats foods, an adherence to RFS and MED diet were associated with reduced risk of CRC. Among females, results were inconsistent; meat and potatoes pattern was associated with increased risk but neither MED nor RFS had a significant association.

In the Nurse's Health Study (230) index-based score, AHEI (Alternate Healthy Eating Index) was associated with lower levels of free oestradiol while no association was found with the patterns identified by factor analysis. In the Health Professionals Follow-up Study cohort, the risk of incident fatal or nonfatal myocardial infarction and stroke (CVD) in the highest quintile of the HEI, alternate HEI, and RFS, respectively, were 28%, 39%, and 23% lower (231) than the reference quartile, while the highest quintile of a prudent diet score from factor analysis was 30% (232). While estimating the survival outcome using different diet pattern, a prospective Danish observational study (233) showed that a prudent diet pattern obtained by PCA was associated with reduced mortality but index-based patterns had no significant association. In the EPIC Potsdam study, neither index-based nor factor analysis had a significant association with hypertension (234). In the SENECA study; the index based scales including Mediterranean Diet Score (MDS), the Mediterranean Adequacy Index (MDI) and the Healthy Diet Indicator (HDI) showed an inverse association with all-cause mortality (235).

The current study suggested good evidence of comparability between PCA and CA in identifying the diet pattern as seen in other studies (236, 237) despite their different approach. Almost two-thirds of individuals in the fruit and vegetable cluster (Cluster I)

were from the highest quartile of the prudent vegetable pattern identified by PCA having highest loading (>0.50) for fruits, vegetables, greens, tomatoes and minimal loadings (<0.15) for processed meat, red meat and refined foods. More than 90% of individuals in Cluster II, characterized by meat and dairy products, were from the highest quartile of the processed meat pattern identified by PCA had higher loading (>0.5) for red meat, cured processed meat. Similar was the case with other clusters. Despite good evidence of comparability, they aren't defined by the same foods, which is likely to be the reason for differential disease outcome estimate.

Hypothesis-driven diet patterns give higher weight for fruits and vegetables, which is evident by having the majority of individuals in the lowest quartile of DII and the highest quartile of Alt-Med and RFS in Cluster I, characterized by fruits and vegetables. Correlations between index scores were relatively strong and statistically significant as scores were based on similar food recommendations. An increasing score of Alt-Med, RFS and a decrease in DII score are characterized by the higher amount of plant-based food (238).

Indexing systems vary in the definition of optimal diet quality and in their scoring which leads difference in their sensitivity to estimate the disease outcome. Differential classification of food leads to differential exposure. RFS accounts for intake of vegetables, fruits, healthy protein sources, grains and dairy products but does not differentiate between different types of fatty acids or penalize for consumption of foods that are not recommended. Alcohol, energy-dense foods and meat products, which are all associated with survival outcomes according to the empirical approaches used to

investigate the population are not considered in scoring. Hence, RFS is likely to underestimate the true association. Further, in the RFS approach, energy cannot be adjusted so the effect of body size, physical activity and higher basal metabolic rate cannot be taken into account for the analysis (239). Energy adjustment may also help to reduce measurement error (229). Alt-Med scoring is based on a high consumption of fruits, vegetables, non-refined bread and cereals, legumes and nuts, and a moderate consumption of fish, poultry and alcohol. High intakes of red meats, and processed meats and saturated fat is penalized during scoring (228). The DII score is based on the inflammatory potential of nutrient/food items in response to six inflammatory biomarkers. DII may be relevant for diseases associated with chronic inflammation (34). DII is not only limited to micro and macronutrients but also incorporates commonly used bioactive compounds including flavonoids, spices and tea. Since the current study was based on pre-diagnostic diet pattern and dietary-induced inflammation may not have a significant role in the survival estimation.

Multiple reasons could be suggested for the inconsistent results; firstly multiple studies have suggested dietary guidelines has been seen strongly related to coronary heart disease than to cancer mortality, even when though guidelines are directed toward lowering cancer risk (240). Extensive studies are done on diet-cardiovascular disease then than cancer, the role of dietary components in cancer causation is still unclear in many instances (231). Secondly, dietary guidelines are more effective for cancer incidence than the survival (and therefore mortality) due to the other clinic-pathological factors in determining the cancer survival (240). Third, the inconsistency might also be due to

missing of some important components and some components in the scales may not have the significant association with the cancer risk and survival (231).Also, our approximation of the three scales varied slightly than the original scale. Original RFS had 23 items and was developed for the all-cause mortality rather than cancer-specific mortality (32). Likewise, Alt-Med score was developed to assess the variations in the biomarkers level (241) and DII index was based on 45 different food parameters whilst the current study had only 28 parameters(34).

Each method has its own strengths and limitations (27). Empirical methods are an initial approach and identify diet patterns as they exist in the population (179) and form the basis for index-based patterns, but suffer certain limitations: (a) They are based on eating behaviour rather than the biological plausibility hence the diet pattern may not exactly reflect disease causation theory (179); (b) Even though an association is detected, it may not represent beneficial or detrimental eating patterns (242); (c)Lacks limited reproducibility across the studies (25) and (d)Includes several arbitrary decisions including consolidation of food items into food groups, number of factors/clusters, method of rotations and labelling of the patterns/clusters (243). Index-based patterns are based on adherence to the recommendation or guidelines and the foundation of each scale varies. Index-based patterns are generally considered by many to be better at estimating the disease outcome as compared to empirical patterns due to their inclusion of relevant and evidence-based components (234). It has been claimed that results are more reproducible across studies. However, they are limited in that they do not capture a full

range of diets in scoring (179) and are difficult to use when scores do not vary considerably within the population (27) and results vary with the cut-offs defined.

Strengths and Limitations of study

This is a prospective follow-up study. Detailed data for the variables (age; sex; marital status; Body Mass Index; screening history; use of medications; co-morbidity status; history of CRC; smoking; physical activity; diet patterns; alcohol intake; stage and location of tumor; chemotherapy status; etc.) are available including the genetic data on MSI status. Multiple diet patterns are used for comparison.

This study has a number of limitations. First, the sample is relatively small, which may not offer desirable statistical power and precision in multivariate analysis. Further, cases were followed until 2010 only. Recall error and possible bias are likely to exist as the cases were asked to remember their diet patterns a year prior to their diagnosis. However, we believe the recall bias, if any, could be non-differential, which is likely to attenuate the observed association. Although bias may exist and sample size is less, it may have little impact on cross-comparison, which is the primary focus of the study. Some cases might have changed their diet patterns, lifestyle and behaviour after diagnosis or even in the disease induction/latent period; this may lead to possible reverse causation bias, which should be explored in future studies.

Conclusions

The present study showed that the estimation of OM and DFS amongst the CRC patients varied with the type of diet pattern used. Hazards ratios for DFS varied from 1.82; 95% (CI- 1.07-3.09) for processed meat pattern identified by PCA to HR 2.19; 95% CI 1.03-4.67 for cluster characterized by meat and dairy products and HR 1.95; 95% CI 1.13-3.37 for cluster characterized by refined grains, sugar, soft drinks. Only cluster characterized by refined grains, sugar, soft drinks had higher risk of OS (HR 2.05; 95% CI 1.18-3.57). All the diet indices showed similar null associations with both DFS and OS except Poor adherence to altMED increased the risk of all-cause OS (HR 1.62; 95% CI 1.04-2.56). On the average estimates were higher for data driven methods than hypothesis driven. The variations in the estimated hazards ratios is attributed to the foundation of each dietary pattern identified by various approaches.

Abbreviations

Alt-Med: Alternative Mediterranean Diet **BMI:** Body Mass Index

CA: Cluster Analysis **CRC:** Colorectal Cancer **DFS:** Disease Free Survival

DII: Dietary inflammatory Index **FHQ:** Family History Questionnaire

FFQ: Food Frequency Questionnaire **HRT:** Hormone Replacement Therapy

MUFA: Monounsaturated Fatty Acid **NFCCR:** Newfoundland Familial Colorectal Cancer Registry **NL:** Newfoundland and Labrador **NSAID:** Non-steroidal Anti-Inflammatory Drug **OR:** Odds Ratios **OS:** Overall Survival

PCA: Principal Component Analysis **PHQ:** Personal History Questionnaire **PUFA:** Polyunsaturated fatty acid **RFS:** Recommended Food Score **CI:** Confidence interval

Decelerations

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Author's Contribution PW and IS conceived and designed this study. IS analysed the data and drafted the manuscript. PPW, BR, YZ, JW, PSP and JRM revised the manuscript. All authors read and approved the final manuscript.

Conflict of Interest: Authors have no conflicts of interest associated with this study.

Ethics approval and consent to participate

This study is part of the larger project which was approved by the HREB (Health Ethics Review Board) of Memorial University of Newfoundland, Canada. All patients included in this study signed informed consent forms, and data collection followed Declaration of Helsinki guidelines.

Consent for publication

Not applicable

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CHAPTER 4: SUMMARY

With the objective of assessing and comparing different diet patterns while estimating the CRC risk and Patient's survival in the Newfoundland Colorectal Cancer Cohort, the following study was conducted. The following thesis has two major components.

The first part investigated the role of diet-mediated inflammation assessed by DII score on the risk of CRC. DII score is calculated based on 28 food parameters. Individual's diet was classified either pro-inflammatory or anti-inflammatory based on their dietary intake. Results showed that pro-inflammatory diets were associated with increased risk of CRC; suggesting an important role of diet-mediated inflammation in colorectal carcinogenesis. Diet patterns characterized by higher amounts of fruits, vegetables, whole grains, and moderate alcohol intake has lower inflammatory potential and is suggested to reduce the chronic inflammation and subsequently reduced the risk of CRC. Diet pattern higher in refined and processed foods, red meat, sugary items, oils and fats are pro-inflammatory and increases the risk of CRC.

The second part assessed and compared different diet patterns identified by data and hypothesis-driven techniques with CRC patient's survival. Data from 169-item FFQ were used to identify four clusters (identified by CA), three factors (identified by PCA) and three indexes (Alt-Med, RFS and DII). Disease estimation varied with the type of diet pattern used as an independent variable. Processed meats pattern identified by PCA, clusters characterized by meat-dairy-products, total-grains-sugar-soft drinks and poor adherence to Mediterranean diet are associated with poor survival. Prudent vegetable,

high sugar pattern, adherence to recommended food and dietary inflammation index had no significant association with survival. The magnitude of the HRs varied accordingly.

There are no specific criteria to determine which method is superior. Data-driven patterns identify diet patterns as they exist within the population, generate the hypothesis and act as the foundation for index-based patterns. Index-based patterns are considered to be superior due to the inclusion of relevant and evidence-based food items and, evaluate specific dietary goals. Comparing disease outcomes across diet patterns is recommended to better understand diet-disease interactions.

There are some limitations to this study. First, dietary supplements were not considered for the study. Second, there are higher chances of recall bias as the food frequency was collected before the diagnosis or a year before the date of data collection in controls. The major limitation of the second study is the lack of information on the cause of death for all deceased participants. The observed differences in OS and DFS could be deaths from causes other than CRC. Meanwhile, DII score is a new and fairly effective measure to assess the diet mediated-inflammation.

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Appendix

Appendix 1: Food Groupings

FG	Food Groups	Items
FG1	Milk	Whole Milk, 2% Milk, 2% Evaporated Milk, 1% or Skim Milk, Milk Shake
FG2	Yogurt	Yogurt Drink, Yogurt (Plain, 2.4% Fat or More), Yogurt Light (Plain, Less than 2.4% Fat), Yogurt (Fruit Flavoured, Frozen, 2.4% Fat or More), Yogurt Light (Fruit Flavoured, Frozen, Less than 2.4%
FG3	Coffee	Coffee, Coffee (Decaffeinated),
FG4	Tea	Tea, Tea (Herbal)
FG5	Sugar	Sugar in Tea and Coffee
FG6	Soft drinks	Coca Cola, Pepsi, Other Cola, Diet Soft Drinks, Other Soft Drinks (excluding Diet and Cola)
FG7	Egg	Egg (Boiled), Egg (Fried, Scambled, Omelette)
FG8	Cheese	Cream Cheese, Cheese, Cheese, Light (6-15% Fat), Cheese, Ultralight (5% or Less), Cottage or Ricotta Cheese
FG9	Mixed dishes	Soups (Creamed), Pasta (with Meat Sauce), Mixed Dishes with Cheese, Pizza (with Meat), Meat Stew, Chili with Meat or Con Carne
FG10	Red Meat	Ground Beef (Regular), Ground Beef (Medium), Ground Beef (Lean), Roast Beef, Steak, Pork Chop, Roast Pork, Baked Ham, Bacon, Veal, Lamb, Hot Dogs or Wieners, Sausage, Corned Beef, Coldcuts, Liver
FG11	Game	Sea-Birds, Seal, Caribou, Moose, Partridge, Other Wild Birds
FG12	Cured/processed red meat	Baked Ham, Bacon, Hot Dogs or Wieners, Sausage, Corned Beef, Coldcuts, Salted/ Dried Meat, Pickled Meat
FG13	Cured/processed meat	Baked Ham, Bacon, Hot Dogs or Wieners, Sausage, Corned Beef, Coldcuts, Fried Chicken, Salted/ Dried Meat, Pickled Meat, Fried Fish, Canned Fish, Smoked Fish or Lox, Salted or Dried Fish, Pickled Fish
FG14	Polutry	Fried Chicken, Chicken/Turkey, Chicken/Turkey, Skin Removed
FG15	Fish	Shellfish, Fried Fish, Fish (Baked or Broiled), Canned Fish, Smoked Fish or Lox, Salted or Dried Fish, Pickled Fish
FG16	Processed Fish	Canned Fish, Smoked Fish or Lox, Salted or Dried Fish, Pickled Fish

FG17	Fruit Juice	Orange or Grapefruit Juice, Apple or Grape Juice, Other Fruit Juices (Pineapple, Cranberry, etc), Fruit Drink/ Lemonade, Fruit Drinks/ Iced Tea
FG18	Other Fruit	Apples, Pears, Grapes, Bananas, Peaches, Plums, Nectarine, Apricot, Canteloupe, Watermelon, Honeydew Melon, Mango, Papaya, Applesauce, All other Fruit
FG19	Root Vegetables	Potatoes, French Fries and Fried Potatoes, Carrots, Turnips or Rutabagas, Other Root Vegetables
FG20	Cruciferous vegetables	Broccoli, Cabbage, Coleslaw, Cauliflower, Asparagus or Brussel Sprouts
FG21	Other Greens	Spinach / other Green Leafy Vegetables, Green Salad (with Lettuce)
FG22	Beans, peas	Peas or Lima Beans, Green Beans, Beans or Lentils, Pea Soup
FG23	Tomato Sauce	Tomatoes (Fresh), Tomatoes (Canned, Pureed, Sauce), Ketchup
FG24	Other Vegetables	Corn, Cucumber, Onions (Raw or Cooked), Beets (Boiled or Pickled) Yellow Squash, Zucchini or eggplant, Sweet Pepper, Bean Sprouts, Alfalfa Sprouts, Avocado, Other Vegetables (Celery, Mushrooms
FG25	Total Cereals and Grains	Bran or Granola Cereals, Whole Wheat Cereals, Cereals, Not Sugar Coated, Hot Cereals, Sugar Coated Cereals, Other Breakfast Cereals, Sugar on Cereal, 100% Whole Grain or Dark Bread, 60% Whole Grain, Light Rye, White Bread, White Bread Rolls (Including Hot Dog Buns), Whole Wheat Rolls, Crackers, Bran / Oat Muffin, Other Muffin, Pancakes, Waffles, Macaroni, Spaghetti, Noodles, etc, Rice, Crisp Snacks
FG26	Whole grains	Whole Wheat Cereals, 100% Whole Grain or Dark Bread, 60% Whole Grain, Light Rye, Whole Wheat Rolls
FG27	Desserts and sweets	Cakes, Pies and Tarts, Donuts and Sweet Rolls, Cookies, Ice Cream Light or Diet Ice Cream, Pudding, Diet or Light Pudding, JELLO, Popsicles, Freezies, Chocolate Bar and Candy, Candy (without Chocolate)
FG28	Vegetable Juice	Vegetable Juices
FG29	Beer	Beer or Ale
FG30	White wine	White Wine
FG31	Red wine	Red Wine, Sherry, Port(or Other Fortified Wine)
FG32	Liquor	Liquor
FG33	Citrus	Citrus Fruits

FG34	Berries	Berries
FG35	Dried fruit	Dried Fruits
FG36	Canned Fruit	Canned Fruit
FG37	Pies, tarts	Pies and Tarts
FG38	Jam, Jelly	Jam, Jelly, Honey, Syrup
FG39	Pickled Vegetables	Pickles, Relish

Appendix 2: Characteristics of Cluster

Cluster I (157)	**Cluster II (37)**	**Cluster III(99)**	**Cluster IV (253)**
Fruits	Dairy products (Milk, cheese, Yogurt)	Desserts and sweets	Did not indicate any specific distinguishing food as it had no specific dominating food items.
Fruit and Vegetable Juice	Red and Processed meats/fish, game meat	Sugar	
Vegetables, greens	Poultry	Soft Drinks	
Beans, peas	Mixed Dishes	Total grains and cereals	
Whole Grains			
Wine (Red, white)			
Fish (Non-processed)			
Numbers in the parenthesis indicates the cluster size			

Appendix 3: Factor loading and explained variances (VAR)

Food Groups	Processed Meat pattern	Prudent Vegetable pattern	High-Sugar Pattern
Milk		0.19	
Yogurt		0.31	
Sugar		-0.19	0.20
Tea			0.17
Coffee	0.17		
Soft Drinks	0.19		
Cheese	0.15	0.21	
Egg	0.21		0.16
Mixed Dishes	0.31	0.17	0.23
Red Meat	**0.69**		0.17
Cured/processed red meat	**0.73**		0.21
Cured/processed meat	**0.93**		
Game	0.23		
Poultry	0.22	0.27	
Fish	**0.58**	0.32	-0.22
Processed Fish	**0.50**	0.25	
Fruit Juice		0.24	0.23
Root Vegetables	0.28		0.15
Cruciferous vegetables		**0.54**	
Other Fruits		**0.59**	
Other greens		**0.60**	-0.22
Tomato Sauce		**0.50**	
Other Vegetables	0.22	**0.54**	
Beans, Peas	0.15	0.25	
Pickled Vegetables	0.15	0.26	0.15

Total Cereals and Grains	0.23	0.38	0.28
Whole grains		0.33	
Citrus		0.34	
Berries		0.45	
Dried Fruits		0.39	
Vegetable Juice		0.17	
Beer	0.19		
White Wine			
Red Wine			
Liquor			
Desserts and Sweets	0.31		**0.63**
Pies, Tarts	0.15		**0.54**
Canned Fruits		0.21	0.23
Jam, Jelly			0.26
Proportion o f VAR explained (%)	37.79	22.93	11.10
Cumulative VAR Explained (%)	37.79	62.72	73.82

Absolute loadings < 0.15 were not listed for simplicity. Those with loadings of 0.50 or greater are in bold

Appendix 4: Recommended food Score (McCullough ML, et.al; 2002)

Food Group	Foods Included
Vegetables	Potato, Carrot, Broccoli, Cabbage, Cauliflower, Corn, Peas/lime beans, Green beans, Beans/lentils, Spinach, Green Salad, Cucumber, Tomato, Canned Tomato, Onions, Beets, Turnip/rutabagas, Root Vegetables, Yellow Squash, Zucchini/egg plant, Avocado, Veg Juice
Fruit	Apple/pears, citrus fruits, Berries, Grapes, Bananas, (Peaches, Plums, Apricots), Dried Fruits, Apple Sauce, Cantaloupe, Watermelon, Honeydew melon, mango, papaya, fruit juice,
Protein	Chicken/turkey without skin, Shell fish, other fish, canned tuna, tofu
Grains	Bran, whole wheat, hot cereal, cereals, dark bread, whole grains
Dairy	Skim milk
Max. Score	47 (1 point for each item consumed at least weekly)

Appendix 5: Alternate Mediterranean Diet Score (Teresa T Fung, et.al; 2005)

Vegetables	All Vegetables except Potato	Greater than median intake (g/d)
Legumes	Tofu, beans, peas, lentils	Greater than median intake (g/d)
Fruit	All fruit and Juices	Greater than median intake (g/d)
Nuts	Nuts	Greater than median intake (g/d)
Whole Grains	Bran, whole wheat, cereals, hot cereals, dark bread, whole grain	Greater than median intake (g/d)
Red and Processed Meat	Red and Processed Meat	Less than median intake (g/d)
Fish	All fish and shell fish	Greater than median intake (g/d)
Ratio Mono-unsaturated to saturated fat		Greater than median intake
Alcohol		5-25g/d

0 point if the criteria is not met
Maximum Score 9