4-12-2019

The Inflammatory Potential of Diet in Determining Cancer Risk; A Prospective Investigation of Two Dietary Pattern Scores

Stina Bodén
Robin Myte
Maria Wennberg
Sophia Harlid
Ingegerd Johansson

See next page for additional authors

Follow this and additional works at: https://scholarcommons.sc.edu/sph_health_promotion_education_behavior_facpub

Part of the Public Health Education and Promotion Commons
The inflammatory potential of diet in determining cancer risk; A prospective investigation of two dietary pattern scores

Stina Bodén1,*, Robin Myte1, Maria Wennberg2, Sophia Harlid1, Ingegerd Johansson2, Nitin Shivappa3,4,5, James R. Hébert3,4,5, Bethany Van Guelpen1,6, Lena Maria Nilsson2,7

1 Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden, 2 Department of Public Health and Clinical Medicine, Sustainable Health/Nutritional Research, Umeå University, Umeå, Sweden, 3 Cancer Prevention and Control Program, University of South Carolina, Columbia, SC, United States of America, 4 Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC, United States of America, 5 Connecting Health Innovations LLC, Columbia, SC, United States of America, 6 Wallenberg Centre for Molecular Medicine, Umeå University, Umeå, Sweden, 7 Arcum, Arctic Research Center at Umeå University, Umeå, Sweden

*stina.boden@umu.se

Abstract

Purpose
Inflammation-related mechanisms may contribute to the link between diet and cancer. We sought to investigate the inflammatory impact of diet on cancer risk using the Dietary inflammatory index (DII) and an adapted Mediterranean diet score (MDS).

Methods
This population-based, prospective cohort study used self-reported dietary data from the Västerbotten Intervention Programme, including 100,881 participants, of whom 35,393 had repeated measures. Associations between dietary patterns and cancer risk were evaluated using Cox proportional hazards regression. We also used restricted cubic splines to test for potential non-linear associations.

Results
A total of 9,250 incident cancer cases were diagnosed during a median follow-up of 15 years. The two dietary patterns were moderately correlated to each other and had similar associations with cancer risk, predominantly lung cancer in men (DII per tertile decrease: Hazard ratio (HR) 0.81 (0.66–0.99), MDS per tertile increase: HR 0.86 (0.72–1.03)), and gastric cancer in men (DII: 0.73 (0.53–0.99), MDS: 0.73 (0.56–0.96)). Associations were, in general, found to be linear. We found no longitudinal association between 10-year change in diet and cancer risk.

Conclusion
We confirm small, but consistent and statistically significant associations between a more anti-inflammatory or healthier diet and reduced risk of cancer, including a lower risk of lung
Introduction

A third of all cancer-related deaths may be linked to diet [1] and inflammation-related mechanisms may be involved [2]. A pro-inflammatory diet estimated by higher Dietary inflammatory index (DII) scores has been associated with both systemic low-grade inflammation and increased risk of cancers including prostate, breast, colorectal, lung, and pancreas [3–6]. Excess body fat is an established risk factor for many types of cancers [1]. An energy-dense diet may induce weight gain, which can lead to a pro-inflammatory state, but also could increase cancer risk through an altered sex hormone profile [7]. Adherence to a Mediterranean diet, represented by a higher Mediterranean diet score (MDS) [8], has been associated with both lower levels of inflammatory biomarkers and lower risk of several types of cancer [9]. The high dietary intake of antioxidants, including polyphenols, associated with higher adherence to the Mediterranean diet, may inhibit multiple cancer-related biological pathways [10]. Thus, defining a dietary pattern to distinguish between inflammation and other mechanisms by which the diet might influence cancer risk, is desirable.

The aim of this study was to investigate the inflammatory impact of diet in determining cancer risk using two widely used indices, the inflammation-specific DII and an adapted MDS. These dietary indices were examined in 9,250 prospective cancer cases in a population-based cohort of 100,881 participants, including 35,393 individuals with repeated measures ≥ 10 years apart.

Methods

Study cohort and study population

Study participants were selected from the Västerbotten Intervention Programme (VIP) cohort, an ongoing population-based, prospective cohort in northern Sweden, established in 1986 [11]. During a decennial health examination, residents 40, 50, and 60 years of age (also 30 years during 1990–1996), were asked to complete a questionnaire on diet and lifestyle and to donate a blood sample. This study included 100,881 participants (50.6% women) with data from Feb. 15, 1990 (excluding the first few years of the cohort, with less-standardized FFQs) to Jan. 19, 2016 (Fig 1). All participants were followed until either diagnosis of an invasive cancer or until end of follow-up on Nov. 10, 2016. Exclusion criteria were previous cancer diagnosis other than non-melanoma skin cancer, insufficient dietary data, implausible food intake levels (FIL) (below the 1st or above the 99th percentile for each version of the food frequency questionnaire (FFQ) and for each sex), implausible energy intakes (below the 1st percentile or >5000 kcal/day), implausible anthropometric data (height <130 cm or >210 cm, weight <35 kg or body mass index (BMI) <15 or >70 kg/m²), and cancer cases diagnosed within 1 year of their last measurement (n = 605).

We also estimated associations between 10-year changes in dietary pattern scores and cancer risk. Participants with health examinations deviating by more than ±2 years from the VIP age groups or more than ±2 years from the 10-year time span between health examinations, were excluded. For participants with three measurements (n = 7,118), the two earliest measurements were used. After exclusions (n = 2,135), a total of 35,393 participants were included in the longitudinal analyses.
Dietary data were harmonized and refined by the Northern Sweden Diet Database (NSDD) management. Validated FFQs—a longer version with 84 items and a shortened version of the same FFQ with 64–66 items—were used to calculate dietary pattern scores [12–14]. Food items, reported on a fixed, nine-option scale ranging from never to ≤4 times/day, were converted into daily intakes (g/day) using reported portion sizes combined with data from the

Dietary data

Dietary data were harmonized and refined by the Northern Sweden Diet Database (NSDD) management. Validated FFQs—a longer version with 84 items and a shortened version of the same FFQ with 64–66 items—were used to calculate dietary pattern scores [12–14]. Food items, reported on a fixed, nine-option scale ranging from never to ≥4 times/day, were converted into daily intakes (g/day) using reported portion sizes combined with data from the
National food composition database [15]. For nearly all repeated measures (99.8%), and 67.5% of the baseline measurements, the participants filled out the shorter FFQ.

**Dietary inflammatory index**

Detailed descriptions of development and scoring algorithm of the DII [3], as well as construct validations can be found elsewhere [4, 5]. Briefly, nearly 2000 articles investigating the relation between specific dietary factors and six different inflammatory markers (interleukin (IL)-1β, IL-4, IL-6, IL-10, tumor necrosis factor alpha and CRP (C-reactive protein)) were reviewed. A total of 45 specific foods and nutrients were indexed and scored to derive an inflammatory effect score for each parameter. Dietary data were linked to a database including eleven data-sets covering most regions of the world, from which means and standard deviations for the 45 food parameters were derived. These parameters were then used as multipliers to express an individual’s exposure relative to the “standard global mean” as a z-score, by subtracting the “standard global mean” from the reported amount and dividing the difference by the standard deviation. The value was converted to a centered proportion score for each food parameter and subject, and multiplied by the corresponding food parameter effect score to produce a food parameter-specific DII score. In this study, 30 of the original 45 foods and dietary components were available for calculation, thus 15 food parameters were lacking (listed in S1 Table), a proportion similar to that observed in other observational studies using the DII [16–18].

**Mediterranean diet score**

The Mediterranean diet is characterized by high intake of vegetables, legumes, fruits, nuts, seeds, cereals, and olive oil, moderately high intake of fish, low to moderate intake of dairy products, moderate intake of alcohol, and low intake of saturated fat, meat and meat products [8]. We used an adapted version of the MDS previously applied in Swedish populations based on existing knowledge about positive health effect of whole-grain cereals, moderate alcohol intake, and also that polyunsaturated fatty acids (PUFA) and not only monounsaturated fatty acids (MUFA) are important unsaturated fats in non-Mediterranean countries [19]. The adapted MDS has eight components (listed in S1 Table), 1) vegetables and potatoes, 2) fruit and fresh juices, 3) wholegrain cereals, 4) fish and fish products, 5) ratio of MUFA + PUFA to saturated fat (SFA), 6) alcohol intake, 7) meat and meat products, and 8) dairy products. The intake of each component was adjusted to daily energy intakes of 2500 kcal for men and 2000 kcal for women, using the nutrient density method (e.g., component/total energy). For components 1–6, a value of 1 was assigned to subjects whose consumption was higher than the sex- and FFQ-specific median and 0 for intakes below the median, except for alcohol where participants with intakes < 50g/day were assigned 1, and 0 if > 50g/day. For meat and dairy products, a value of 1 was assigned for subjects with intakes below the median. The summed MDS ranges from 0 (low adherence) to 8 (high adherence).

**Covariates**

Smoking status was classified as daily smoker, ex-smoker (former daily smoker), or never smoker (including occasional smoker and former occasional smoker). Diabetes was defined as self-reported or diagnosed at the health examination according to fasting blood glucose (≥ 7.0mmol/L) or 2-hour post-load plasma glucose (≥ 12.2mmol/L in capillary blood). BMI (kg/m²) was calculated using measurements taken by a health care professional. Physical activity refers to recreational physical activity, harmonized between questionnaire versions and classified in three levels: low (no recreational physical activity exercise), medium (up to 2 times a week), and high (≥ 3 times a week). Educational status was defined at three levels; elementary
school (including lower secondary, up to 9 years of school), upper secondary school or post-secondary education. Total energy intake was calculated from FFQ-derived dietary data and expressed as kcal/day.

Identification of cancer cases

Cancer endpoints were identified by linkage to the essentially complete regional branch of the Swedish Cancer Registry. Cases were defined based on ICD-10 codes as first incident malignancy (all types), as well as first incident breast (C50), prostate (C61), lung (C34), gastric (C16), pancreas (C25), colorectal (C18-C20.9), and gastrointestinal (GI) including: esophagus (C15), gastric (C16), liver/intrahepatic bile ducts (C22), pancreas (C25) and small intestine (C17) cancer. We also investigated smoking-related and obesity-related cancers. Smoking-related cancers were defined according to the International Agency for Research on Cancer (IARC) [20]. Tumor sites for which evidence of a link to tobacco smoking is suggested to be sufficient, are: lip/oral cavity/pharynx (C00-C14), liver/intrahepatic bile ducts, larynx/trachea/bronchus/lung (C32-C34), cervix (C53, D06), colorectum, kidney (C64), esophagus, pancreas, stomach, urinary bladder (C67), as well as acute and chronic myeloid leukemia (C91-95 and D46, excluding C91.4)[20]. Obesity-related cancers were defined as cancer of the esophagus, gastric, colorectum, liver, gallbladder (C23-24), pancreas, breast (post-menopausal, approximated as breast cancers diagnosed after the age of 55 years), endometrium (C54), ovary (C56), kidney, meningioma (C70.0), thyroid (C73), and multiple myeloma (C90.0) [7]. Non-smoking-related and non-obesity-related cancers were defined as all other cancers not included in these definitions.

Ethics

This study was approved by the Regional ethical review board of northern Sweden (Dnr 2013/332–31). All study subjects provided written informed consent at recruitment for all collection for research purposes, and the study was conducted in accordance with the Declaration of Helsinki.

Statistical analyses

Baseline characteristics of men and women were calculated for sex- and FFQ-specific categories approximating tertiles of the dietary pattern scores. DII tertiles (T) were constructed according to the distribution of participants. MDS tertiles were distributed to avoid ties: T1) Score 0–3, T2) Score 4, and T3) Score 5–8. Comparisons were made using Pearson Chi-square tests for categorical variables and ANOVA for continuous variables. Correlations between dietary patterns were estimated with Spearman’s correlation coefficient.

Associations between baseline dietary patterns and cancer risk were evaluated using Cox proportional hazards regression with age as the time scale. The proportional hazards assumption was checked by evaluating Schoenfeld residuals. In the all-cancer risk analysis, sex showed signs of non-proportionality characterized as a higher risk of cancer in women compared to men before age 67 years and the opposite after age 67. Therefore, risk estimates are presented for all participants, stratified by sex within the Cox model, but also for men and women separately. In the analysis of breast and lung cancer, both BMI and smoking showed signs of non-proportionality. Because stratification for BMI categories or smoking status did not affect risk estimates, estimates from non-stratified models are presented.

To facilitate comparisons between risk estimates, linear associations are presented as hazard ratios (HR) per tertile decrease in DII or tertile increase in MDS, obtained by modelling continuous scaled variables, i.e. by dividing each dietary pattern score by its respective sex- and
FFQ-specific intertertile range. The mean intertertile ranges were 1.7 for DII and 2 for MDS. Estimates were adjusted for covariates with a potential association to both dietary pattern and cancer risk: energy intake, BMI, physical activity, smoking, and educational status. In sensitivity analyses, HRs were estimated separately by age groups (30–40, 50, and 60 years), smoking status (non smokers, ever smokers), and BMI (BMI >30kg/m², BMI <30kg/m²). HRs were also estimated by excluding participants with diabetes. Heterogeneity in HR estimates between subgroups were tested with a Wald’s test.

To test for non-linear associations, continuous dietary pattern variables were modelled using restricted cubic splines (with knots at the 5th, 50th, and 95th percentiles). Tests for associations were made with a likelihood ratio test comparing the dietary pattern spline model with a model without the dietary pattern. Non-linearity was tested with a likelihood ratio test comparing the spline model to a linear model.

To assess the predictive accuracy of the dietary patterns, we estimated Harell’s C-index in Cox-models using the baseline measurement. C-indices were calculated using ten-fold cross-validation to avoid overfitting.

We evaluated longitudinal associations between dietary patterns and cancer risk by fitting Cox models with start of follow-up 1 year after the repeat measurement, using age as the time scale. Participants were classified as “Unchanged healthy”, “Changed unhealthy to healthy”, “Changed healthy to unhealthy”, or “Unchanged unhealthy” according to baseline and repeat values on dichotomous dietary pattern variables (“unhealthy” defined as DII T3 and MDS T1, using sex- and FFQ-specific cut-offs). We also evaluated longitudinal associations between continuous change in dietary pattern score (Δ = repeat–baseline) and cancer risk. HRs per ter- tile decrease in ΔDII or tertile increase in ΔMDS were obtained by modelling continuous scaled difference variables (i.e., by dividing each Δ-variable by their respective sex- and FFQ specific intertertile ranges) in Cox models. Estimates were adjusted for baseline and Δenergy intake, baseline and ΔBMI, smoking (non-smoker, ex-smoker, stopped smoking, started smoking, continued smoking), physical activity (unchanged, decreased less activity, more physical activity), and baseline educational status.

All computations were conducted in R v.3.4.2 (R Foundation for Statistical Computing, Vienna, Austria). All tests were 2-sided, and P-values <0.05 were considered statistically significant.

Results
Baseline characteristics
Characteristics of the 100,881 study participants at first visit are presented in Table 1. Mean age at baseline increased across tertiles of MDS from 45.2 to 48.0 years for men (P <0.001) and from 44.3 to 48.7 for women (P <0.001). Mean age was more similar across DII tertiles, though P <0.001. Obesity was more common among men with a more pro-inflammatory diet as estimated by the DII (P <0.001), and among both men and women with low adherence to MDS (P <0.001). Participants with higher DII and lower MDS scores (i.e. more pro-inflammatory/unhealthier diet), were less likely to be married or co-habitating, to have post-secondary education or to be physically active, but more likely to be current smokers (P <0.001 for all). Additionally, they were less likely to have been diagnosed with diabetes (DII men P = 0.007, DII women P = 0.03, MDS men P<0.001, MDS women P<0.001).

Baseline DII and MDS scores were moderately negatively correlated (r = -0.34, P<0.001) and correlations were similar for the repeat measures (S2 Table).
Baseline associations between dietary patterns and cancer risk

During follow-up (median 15 years), 9,250 prospective cancer diagnoses were detected, 4,830 in men and 4,420 in women. Linear HRs for cancer by baseline dietary pattern scores, adjusted for potential confounders, are presented in Fig 2. Lower DII, and higher MDS, were weakly associated with a lower risk of cancer (HR (95% CI) per tertile decrease in DII: 0.97 (0.94–0.99), HR per tertile increase in MDS: 0.97 (0.94–1.00)). DII was associated with reduced risk of lung cancer, which was statistically significant in men (HR per tertile decrease in DII in men: 0.81 (0.66–0.99), in women: 0.89 (0.74–1.08)). Both DII and MDS scores were associated with reduced risk of gastric cancer in men (HR per tertile decrease in DII in men: 0.81 (0.66–0.99), women: 0.89 (0.74–1.08)), HR per tertile increase in MDS: 0.73 (0.56–0.96). Neither dietary pattern was associated with reduced risk of gastric cancer in men (HR per tertile decrease in DII: 0.73 (0.53–0.99), in women: 0.89 (0.74–1.08)). Both DII and MDS scores were associated with reduced risk of prostate cancer in men, breast cancer in women, or GI, colorectal and pancreas cancer in both sexes (Fig 2).

The overall accuracy for predicting cancer for models including age, energy intake, BMI, physical activity, smoking, educational status, and dietary patterns, was similar for the two dietary patterns (C-index = 0.70, Fig 2) and slightly better in men compared to women (C-index 0.73 and 0.66, respectively). None of the dietary patterns markedly improved the prediction accuracy for overall or site-specific cancer risk in either sex. C-index was unmodified when excluding energy intake, for a model limited to variables easily obtainable in a clinical or internet-based “risk calculator” type of setting. Excluding participants with diabetes in sensitivity analyses in this study did not affect the results (S1 Fig).

https://doi.org/10.1371/journal.pone.0214551.t001

Table 1. Baseline characteristics by tertiles of DII and MDS for men (n = 49,880) and women (n = 51,001) in the VIP.

| Characteristic | Men | | | | Women | DII | MDS |
|---------------|-----|---|---|---|------|---|---|
| Men T3 T2 T1 | | | | | | | |
| Proportion of participants, n (%) | 16626 (33.3) | 16628 (33.3) | 16626 (33.3) | 19830 (39.8) | 11472 (22.5) | 18381 (36.0) |
| Dietary score, min,max | 5.35,1.87 | 2.14,0.14 | 0.50, -0.06 | <0.001 | 0.3 | 4 | 5.8 |
| Age, mean±sd | 2616 (15.7) | 2451 (14.7) | 2290 (13.8) | <0.001 | 3048 (15.4) | 1757 (15.1) | 2552(13.9) |
| Obese (BMI ≥30), n (%) | 4090 (24.6) | 3209 (19.3) | 2881 (17.3) | <0.001 | 4554 (23.0) | 2414 (20.7) | 3212 (17.5) |
| No post-secondary education, n (%) | 13517 (80.7) | 12258 (73.7) | 11496 (69.1) | <0.001 | 15848 (79.9) | 8695 (74.5) | 12638 (68.7) |
| Women | | | | | | | |
| Proportion of participants, n (%) | 16999 (33.3) | 17001 (33.3) | 17001 (33.3) | 21148 (41.5) | 11666 (23.4) | 18384 (36.9) |
| Dietary score, min,max | 5.35,1.87 | 2.14,0.14 | 0.50, -0.06 | <0.001 | 0.3 | 4 | 5.8 |
| Age, mean±sd | 2616 (15.7) | 2451 (14.7) | 2290 (13.8) | <0.001 | 3048 (15.4) | 1757 (15.1) | 2552(13.9) |
| Obese (BMI ≥30), n (%) | 4090 (24.6) | 3209 (19.3) | 2881 (17.3) | <0.001 | 4554 (23.0) | 2414 (20.7) | 3212 (17.5) |
| No post-secondary education, n (%) | 13517 (80.7) | 12258 (73.7) | 11496 (69.1) | <0.001 | 15848 (79.9) | 8695 (74.5) | 12638 (68.7) |
Associations between dietary patterns and overall cancer risk in subgroups defined by baseline age, smoking status, and BMI, are presented in S2 Fig. HRs were generally similar across subgroups. In men, the association between DII score and cancer risk appeared stronger in participants aged 30 and 40 years (HRs per tertile decrease in DII: 0.89 (0.80–0.99), but the test of heterogeneity was not statistically significant ($P_{\text{heterogeneity}} = 0.28$).

For smoking-related cancers, lower DII or higher MDS were mainly associated with a decreased risk in ever smokers, with weak evidence of heterogeneity in associations between smoking-related and other cancers ($P_{\text{heterogeneity}} = 0.12$ and 0.03 for ever smokers and non-smokers, respectively (S3 Fig). In contrast, for non-smoking-related cancers, i.e. all cancer sites not included in the group of smoking-related sites, lower DII was associated with a decreased risk in non-smokers, and not in ever smokers ($P_{\text{heterogeneity}} = 0.13$). There were no clear differences in the relation between the risk of obesity- or non-obesity-related cancer and dietary patterns.

HRs for cancer types by DII and MDS in all participants, men, and women, modelled by restricted cubic splines, are presented in S4 Fig. Linear associations could be assumed for all associations except DII and pancreatic cancer risk in men, and MDS and gastric cancer in women ($P_{\text{nonlinearity}} = 0.04$ and 0.02, respectively), presented separately in Fig 3. The association for pancreas cancer manifested as a possible lower risk in men with high, and to a lesser extent low, DII compared to the median ($P_{\text{association}} = 0.09$). The suggested nonlinear association between MDS and gastric cancer risk in women was U-shaped, with increased risk at low or high MDS compared to the median ($P_{\text{association}} = 0.06$).
Fig 3. Hazard Ratios (HRs) (black line) and 95% confidence interval (CI) (gray area) of pancreas cancer in men by DII, and gastric cancer in women by MDS. HRs were calculated with restricted cubic splines (with knots on the 5th, 50th, and 95th percentiles) in Cox regression models using attained age as time scale. Presence of an association were tested with a likelihood ratio test comparing the dietary pattern spline model with a model without dietary pattern. Nonlinearity was tested with a likelihood ratio test comparing the spline model to a linear model. The HRs were adjusted for energy intake, BMI, physical activity, smoking, and educational status.

https://doi.org/10.1371/journal.pone.0214551.g003

|          | N_cancer | HR (95% CI) | P_association | P_nonlinearity |
|----------|----------|-------------|---------------|----------------|
| **ALL**  |          |             |               |                |
| Unchanged healthy | 1170 | Reference | 1.00 (0.87–1.14) | 324 | 1.01 (0.89–1.14) |
| Changed unhealthy to healthy | 337 | 1.10 (0.96–1.26) | 394 | 0.99 (0.88–1.12) |
| Changed healthy to unhealthy | 305 | 1.09 (0.95–1.25) | 585 | 1.08 (0.95–1.18) |
| Unchanged unhealthy | 451 | 0.99 (0.95–1.04) | 2263 | 1.03 (1.00–1.06) |
| HR per 1 tertile change | 2263 |             |               |                |
| **Men**  |          |             |               |                |
| Unchanged healthy | 628 | Reference | 1.10 (0.92–1.32) | 155 | 1.10 (0.92–1.32) |
| Changed unhealthy to healthy | 185 | 1.16 (0.96–1.39) | 243 | 1.06 (0.91–1.23) |
| Changed healthy to unhealthy | 173 | 1.12 (0.93–1.34) | 306 | 1.11 (0.96–1.28) |
| Unchanged unhealthy | 245 | 0.99 (0.93–1.05) | 1231 | 0.99 (0.93–1.06) |
| HR per 1 tertile change | 1231 |             |               |                |
| **Women** |          |             |               |                |
| Unchanged healthy | 542 | Reference | 0.98 (0.80–1.20) | 169 | 0.92 (0.77–1.10) |
| Changed unhealthy to healthy | 152 | 1.05 (0.85–1.31) | 151 | 0.91 (0.75–1.09) |
| Changed healthy to unhealthy | 132 | 1.08 (0.89–1.32) | 279 | 1.01 (0.87–1.18) |
| Unchanged unhealthy | 206 | 0.98 (0.92–1.05) | 1032 | 1.04 (1.00–1.08) |
| HR per 1 tertile change | 1032 |             |               |                |

Fig 4. Hazard Ratios (HRs) and 95% confidence interval (CI) for cancer per tertile or category of 10-year change (Δ) in dietary patterns DII and MDS estimated in VIP participants with repeat measurements (n = 35,393). HRs were obtained from Cox regression using age as time scale, with start of follow-up 1 year after the repeat measurement. Categorical variables were defined according to baseline and repeat values on dichotomous dietary pattern variables (“unhealthy” defined as DII 3rd tertile, MDS 1st tertile, using sex- and FFQ specific cut-offs). HRs per tertile change (decrease in ΔDII, and increase per ΔMDS) were calculated by modelling continuous Δ-variables scaled by dividing by the intertertile range (mean intertertile ranges: ΔDII = 1.3, ΔMDS = 1.5). Estimates were adjusted for baseline and Δenergy intake, baseline and ΔBMI, smoking (baseline non-smoker, baseline ex-smoker, stopped smoking, started smoking, or continued smoking), physical activity (unchanged, less activity, more physical activity), and baseline educational status.

https://doi.org/10.1371/journal.pone.0214551.g004
Longitudinal associations between dietary patterns and cancer risk

Moderate correlations were observed between the baseline and repeat measurement for each dietary pattern \((r = 0.40 \text{ to } 0.53)\) (S2 Table). Most participants remained in the same tertile of dietary pattern distribution over the 10-year period (S5 Fig).

Participants, primarily men, with an unchanged, more pro-inflammatory diet at follow-up, as well as participants who went from “healthy” to a more pro-inflammatory diet over the 10-year period were at a slightly increased risk for cancer; however, the association was attenuated and not significant after adjusting for change in BMI and smoking status (Fig 4). A similar pattern was observed for MSD in men, but the association also attenuated and was not significant in the multivariable model.

Ten-year change in DII was not associated with the risk of cancer (HR per tertile decrease in \(\Delta\)DII: 0.99 (0.95−1.04) (Fig 4). Participants with greater \(\Delta\)MDS had a slight increased risk of cancer (HR per tertile increase in \(\Delta\)MDS: 1.03 (1.00−1.06)). Although the sample size was insufficient to detect heterogeneity between cancer types, the finding appeared to be driven primarily by breast cancer in women (S3 Table).

Discussion

In this prospective, population-based study, the DII and the MDS were moderately correlated to each other and produced similar associations with the risk of cancer. An anti-inflammatory or healthier diet was weakly associated with a reduced overall cancer risk, most evident for lung and gastric cancer. Ten-year change in dietary pattern score was not related to cancer risk.

These results are consistent with previously observed positive associations between the inflammatory potential of diet and risk of gastric cancer [21, 22], and the inverse association with a Mediterranean diet [23]. Given the divergent incidence trends for specific subtypes of cancer in the upper gastrointestinal tract [22, 24], further investigation including data on anatomical location of the tumor, histological subtype and \textit{Helicobacter pylori} infection in relation to diet are warranted [25]. Our null results for colorectal cancer were surprising, given the wealth of evidence for a role of diet quality in determining risk [23, 26, 27]. Potential associations between diet and any cancer are likely to be mediated in part by body fatness [7]. However, in the present study, “obesity-related cancer”, demonstrated no clear association with dietary indices. Removing BMI from the model did not change the risk estimates and thus, mediation by body fatness is unlikely to entirely explain the null results. Both consumption of foods generally considered unhealthy and total energy intake are underreported to a greater degree by obese compared to non-obese people [28], which might bias potential associations between diet and obesity-related cancers toward the null.

We observed a general association between a more anti-inflammatory/healthier diet and lower risk of lung cancer, consistent with previous findings [6, 23, 29]. Effect sizes were similar in men and women, but the association for DII score was statistically significant in men only. A plausible explanation for associations found between the dietary patterns and “smoking-related cancer” in ever smokers might be a synergistic effect of smoking and unhealthy dietary habits that increases low-grade chronic inflammation, as previously shown for lung cancer [30, 31].

The null findings for prostate and breast cancer contrast with results from meta-analyses of DII [6, 23]. However, there is considerable inconsistency in results for dietary patterns in relation to these cancer types in previous studies conducted in Nordic populations [32–34]. For breast cancer, the strong risk conferred by reproductive factors, which we were unable to adjust for, might explain the fairly weak and inconsistent results for the DII [35, 36].
The study population did not alter its dietary habits substantially according to our supplementary analysis of longitudinal changes in DII and MDS, which probably explains the fairly consistent results for the longitudinal analyses compared to baseline. Interestingly, a change toward better adherence to the MDS, was associated with an increased cancer risk, primarily in women. This might be due to residual confounding by socioeconomic status, not sufficiently captured by the education variable. Higher socioeconomic status is a risk factor for breast cancer, probably acting as a summary marker for factors related to reproduction [37]. Diabetes also was disproportionately common among those with healthier diet and reverse causality due to disease-related dietary changes cannot be excluded [38]. However, excluding participants with diabetes in sensitivity analyses in this study had no material effect on the results.

The fifteen DII food parameters lacking in this study are all considered anti-inflammatory, which might limit the ability of the score to capture an anti-inflammatory diet. However, the range of DII scores in our population is similar to a validation study in an American population based on 44 of the 45 components, which showed a direct association with CRP levels [4].

Nutrients and food components with evidence for a relation to cancer risk are largely covered by both DII and MDS, which undoubtedly contributed to the similar estimates for cancer risk. Whereas the DII was designed specifically to estimate the inflammatory potential of diet [3], the MDS may also capture other mechanisms involved in carcinogenesis, such as reduced free radical production [39] and metabolic function [40]. For example, sugary foods, which can influence blood glucose control and body fatness [40], are considered directly in the MDS but are included only in the broader category of carbohydrates in the DII. Also, red and processed meats, included in the MDS meat component, but not DII, with its high content of salt, N-nitroso, heterocyclic amines, and heme iron have all been implicated in carcinogenesis [41]. Although inflammation may be a common factor in our findings and a major player in explaining the link between diet and cancer, other mechanisms also may be involved.

A weakness in this study is the self-reported dietary intake, which is subject to recall bias and underreporting. Underreporting of socially undesirable foods has been documented, especially in women [42] and obese people [28], and constitutes a possible bias. However, the FFQs had acceptable reproducibility and a validity similar to FFQ measurements in other prospective cohort studies [12–14]. The DII is constructed on a continuous scale, whereas the MDS comprises a number of food groups. Thus, approximate tertiles were used to balance between statistical power and dispersion for the specific cancer-sites. The MDS used in this study was adapted for the northern Swedish population in this study [19], and it is thus not fully representative of the traditional Mediterranean diet. For example, since PUFA make up a substantially larger portion of the unsaturated fatty acid intake in the Nordic diet than in the traditional Mediterranean diet [8], the sum of MUFA and PUFA, rather than MUFA alone, was used in the ratio to SFA. Adaptations of the MDS have been successfully applied in various non-Mediterranean populations [43].

Although confounders may differ between cancer types, we applied the same set of covariates in all analyses, in order to simplify interpretation of results. Information about some potential confounders was lacking, such as use of nonsteroidal anti-inflammatory drugs (NSAID), of particular relevance for CRC, and menopausal hormone therapy, of relevance for breast cancer. Many types of cancer demonstrate substantial intertumoral heterogeneity. More specific anatomic location for cancers of the upper and lower gastrointestinal tract, as well as tumor characteristics, such as histological subtype for lung and gastric cancer, hormone receptor status for breast cancer, and microsatellite instability and other molecular traits in CRC could, therefore, add valuable information.
A major strength of this study is its prospective design, with over 100,000 participants and up to 26 years of follow-up. Because exposure data were collected before cancer diagnosis, reverse causality and disease-specific recall bias were unlikely to have influenced the results. Furthermore, repeated measures (10-year intervals) were available for over 35,000 participants, allowing investigation of longitudinal dietary changes in relation to cancer risk. Although these analyses were sufficiently powered to examine overall cancer risk, a larger sample size would be necessary for site-specific cancer. Additionally, with restricted cubic spline models we could show that most associations were linear. Another important strength is the population-based nature of the cohort used, as demonstrated by the very similar cancer incidence in the VIP and the background population [44], as well as the high participation rate (52–73% over the recruitment period) and the low potential for selection bias [45].

In conclusion, in this prospective cohort study, we confirm small, consistent, and statistically significant associations between a more anti-inflammatory or healthier diet and reduced risk of cancer, for lung and gastric cancer in specific, and particularly in men. Although several mechanisms may be involved, the consistency of the findings for the DII, designed specifically to capture the inflammatory impact of diet, and the MDS, suggests that inflammation may be a common denominator.

Supporting information

S1 Table. Food parameters in adapted DII and adapted MDS.
(DOCX)

S2 Table. Spearman’s correlations between DII and MDS at baseline, repeat, and across baseline and repeat measurements.
(DOCX)

S3 Table. Hazard ratios (HRs) and 95% confidence interval (CI) for longitudinal change in DII and MDS for all cancer.
(DOCX)

S1 Fig. Sensitivity analysis excluding participant diagnosed with diabetes. Hazard ratios (HRs) and 95% CI for all cancer per tertile decrease in DII and tertile increase per MDS at baseline.
(DOCX)

S2 Fig. Hazard ratios (HRs) and 95% confidence interval (CI) for all cancer per tertile decrease in DII and tertile increase per MDS at baseline in subgroups defined by age of study entry (VIP age groups ±2), smoking status, and BMI.
(DOCX)

S3 Fig. Hazard ratios (HRs) and 95% confidence interval (CI) for smoking-related and obesity-related cancer per tertile decrease in DII and tertile increase per MDS at baseline in subgroups defined by smoking status and BMI.
(DOCX)

S4 Fig. Restricted cubic splines with hazard ratio (HR) and 95% confidence interval of cancer in a) all participants b) men, and c) women by baseline dietary pattern score.
(DOCX)

S5 Fig. Distribution of 10-year longitudinal changes in dietary patterns.
(DOCX)
Acknowledgments

The authors want to acknowledge all the participants in the VIP, the teams at Region Västerbotten for collecting data and organizing the VIP, and the personnel at the Department of Biobank Research, Umeå University for data maintenance and administrative support. A special thanks to Christel Häggström at the Department of Biobank Research, Umeå, for valuable methodology discussions.

Author Contributions

**Conceptualization:** Stina Bodén, Robin Myte, Maria Wennberg, Nitin Shivappa, James R. Hébert, Bethany Van Guelpen, Lena Maria Nilsson.

**Data curation:** Stina Bodén, Robin Myte, Maria Wennberg, Sophia Harlid, Ingegerd Johansson, Nitin Shivappa, James R. Hébert, Bethany Van Guelpen, Lena Maria Nilsson.

**Formal analysis:** Stina Bodén, Robin Myte, Maria Wennberg, Bethany Van Guelpen, Lena Maria Nilsson.

**Funding acquisition:** Stina Bodén, Ingegerd Johansson, Bethany Van Guelpen.

**Investigation:** Stina Bodén, Robin Myte.

**Methodology:** Stina Bodén, Robin Myte, Ingegerd Johansson, Nitin Shivappa, James R. Hébert, Lena Maria Nilsson.

**Project administration:** Ingegerd Johansson, Bethany Van Guelpen.

**Supervision:** Maria Wennberg, Sophia Harlid, Bethany Van Guelpen, Lena Maria Nilsson.

**Validation:** Robin Myte.

**Visualization:** Stina Bodén, Robin Myte, Bethany Van Guelpen.

**Writing – original draft:** Stina Bodén, Robin Myte, Maria Wennberg, Bethany Van Guelpen, Lena Maria Nilsson.

**Writing – review & editing:** Stina Bodén, Robin Myte, MariaWennberg, Sophia Harlid, Ingegerd Johansson, Nitin Shivappa, James R. Hébert, Bethany Van Guelpen, Lena Maria Nilsson.

References

1. Norat T, Scoccianti C, Boutron-Ruault MC, Anderson A, Berrino F, Cecchini M, et al. European Code against Cancer 4th Edition: Diet and cancer. Cancer Epidemiol. 2015; 39 Suppl 1:S56–66. Epub 2015/07/15. https://doi.org/10.1016/j.canep.2014.12.016 PMID: 26164653.

2. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008; 454 (7203):436–44. Epub 2008/07/25. https://doi.org/10.1038/nature07205 PMID: 18650914.

3. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hebert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. Public Health Nutr. 2014; 17(8):1689–96. Epub 2013/08/15. https://doi.org/10.1017/S1368946513002115 PMID: 23941862; PubMed Central PMCID: PMCPMC3925198.

4. Shivappa N, Steck SE, Hurley TG, Hussey JR, Ma Y, Ockene IS, et al. A population-based dietary inflammatory index predicts levels of C-reactive protein in the Seasonal Variation of Blood Cholesterol Study (SEASONS). Public Health Nutr. 2014; 17(8):1825–33. Epub 2013/10/11. https://doi.org/10.1017/S1368946513002565 PMID: 24107546; PubMed Central PMCID: PMCPMC3983179.

5. Tabung FK, Steck SE, Zhang J, Ma Y, Liese AD, Agalliu I, et al. Construct validation of the dietary inflammatory index among postmenopausal women. Ann Epidemiol. 2015; 25(6):398–405. https://doi.org/10.1016/j.annepidem.2015.03.009 PMID: 25900255
6. Fowler ME, Akinyemiju TF. Meta-analysis of the association between dietary inflammatory index (DII) and cancer outcomes. Int J Cancer. 2017; 141(11):2215–27. Epub 2017/08/11. https://doi.org/10.1002/ijc.30922 PMID: 28795402.

7. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K, et al. Body Fatness and Cancer—Viewpoint of the IARC Working Group. N Engl J Med. 2016; 375(8):794–8. Epub 2016/08/25. https://doi.org/10.1056/NEJMra1606602 PMID: 27557308.

8. Trichopoulou A, Costacou T, Bamia C, Trichopoulou D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med. 2003; 348(26):2599–608. Epub 2003/06/27. https://doi.org/10.1056/NEJMoa025039 PMID: 12826634.

9. Casas R, Sacanella E, Estruch R. The immune protective effect of the Mediterranean diet against chronic low-grade inflammatory diseases. Endocr Metab Disord Drugs Targets. 2014; 14(4):245–54. Epub 2014/09/23. https://doi.org/10.2174/1871530314666140922153350 PMID: 25244229; PubMed Central PMCID: PMCPM24443792.

10. Russo GI, Solinas T, Urzi D, Privitera S, Campisi D, Cocci A, et al. Adherence to Mediterranean diet and prostate cancer risk in Sicily: population-based case-control study. Int J Impot Res. 2018. Epub 2018/10/20. https://doi.org/10.1038/s41443-018-0088-5 PMID: 30337696.

11. Norberg M, Wall S, Boman K, Weinehall L. The Vasterbotten Intervention Programme: background, design and implications. Glob Health Action. 2010; 3. Epub 2010/03/27. https://doi.org/10.3402/gha.v3i0.4643 PMID: 20339479; PubMed Central PMCID: PMCPM2844807.

12. Wennberg M, Vessby B, Johansson I. Evaluation of relative intake of fatty acids according to the Northern Sweden FFQ with fatty acid levels in erythrocyte membranes as biomarkers. Public Health Nutr. 2009; 12(9):1477–84. Epub 2009/01/16. https://doi.org/10.1017/S1368980008004503 PMID: 19144238.

13. Johansson I, Van Guelpen B, Hultdin J, Johansson M, Hallmans G, Stattn P. Validity of food frequency questionnaire estimated intake of folate and other B vitamins in a region without folic acid fortification. Eur J Clin Nutr. 2010; 64(8):905–13. https://doi.org/10.1038/ejcn.2010.80 PMID: 20502473.

14. Johansson I, Hallmans G, Wikman A, Biessy C, Riboli E, Kaaks R. Validation and calibration of food-frequency questionnaire measurements in the Northern Sweden Health and Disease cohort. Public Health Nutr. 2002; 5(3):487–96. Epub 2002/05/11. https://doi.org/10.1079/PHN2001315 PMID: 12003662.

15. Hornell A, Winkvist A, Hallmans G, Weinehall L, Johansson I. Mis-reporting, previous health status and health status of family may seriously bias the association between food patterns and disease. Nutr J. 2010; 9:48. Epub 2010/11/03. https://doi.org/10.1186/1475-2891-9-48 PMID: 21034591; PubMed Central PMCID: PMCPM2988699.

16. Deng FE, Shivappa N, Tang Y, Mann JR, Hebert JR. Association between diet-related inflammation, all-cause, all-cancer, and cardiovascular disease mortality, with special focus on prediabetics: findings from NHANES III. Eur J Nutr. 2016. Epub 2016/01/31. https://doi.org/10.1007/s00394-016-1158-4 PMID: 26825592.

17. Shivappa N, Zucchini A, Montella M, Serraino D, Steck SE, La Vecchia C, et al. Inflammatory potential of diet and risk of colorectal cancer: a case-control study from Italy. Br J Nutr. 2015; 114(1):152–8. Epub 2015/06/09. https://doi.org/10.1017/S0007114515001828 PMID: 26050636.

18. Tabung FK, Steck SE, Zhang J, Ma Y, Liede AD, Tylavsky FA, et al. Longitudinal changes in the dietary inflammatory index: an assessment of the inflammatory potential of diet over time in postmenopausal women. Eur J Clin Nutr. 2016; 70(12):1374–80. Epub 2016/07/07. https://doi.org/10.1038/ejcn.2016.116 PMID: 27380883; PubMed Central PMCID: PMCPMC5143205.

19. Tognon G, Nilsson LM, Lissner L, Johansson I, Hallmans G, Lindahl B, et al. The Mediterranean diet score and mortality are inversely associated in adults living in the subarctic region. J Nutr. 2012; 142(8):1547–53. Epub 2012/06/29. https://doi.org/10.3945/jn.112.160499 PMID: 22739377.

20. Secretan B, Straif K, Baan R, Grosse Y, El Ghissassi F, Bouvard V, et al. A review of human carcinogens—Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol. 2009; 10(11):1033–4. Epub 2009/11/06. PMID: 19891056.

21. Shivappa N, Hebert JR, Ferraroni M, La Vecchia C, Rossi M. Association between Dietary Inflammatory Index and Gastric Cancer Risk in an Italian Case-control Study. Nutr Cancer. 2016; 68(8):1262–8. Epub 2016/11/01. https://doi.org/10.1080/01635581.2016.1224436 PMID: 27366679; PubMed Central PMCID: PMCPMC5154551.

22. Agudo A, Caysials V, Bonet C, Tjonneland A, Overvad K, Boutron-Ruault MC, et al. Inflammatory potential of the diet and risk of gastric cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Am J Clin Nutr. 2018; 107(4):607–16. Epub 2018/04/11. https://doi.org/10.1093/ajcn/nqy002 PMID: 29635497.
28. Shivappa N. Dietary patterns and prospective studies on colorectal cancer risk. Nutr Cancer. 2017; 3390/nu7042589 PMID: 25859884; PubMed Central PMCID: PMCPMC4425163.

30. Shivappa N, Wang R, Hebert JR, Jin A, Koh WP, Yuan JM. Association between inflammatory potential of diet and lung cancer among smokers in a prospective study in Singapore. Eur J Nutr. 2018; 27(7):907–17. Epub 2018/09/27. https://doi.org/10.1007/s10552-018-0725-8 PMID: 30255403.

32. Hodge AM, Bassett JK, Shivappa N, Hebert JR, English DR, Giles GG, et al. Dietary inflammatory index, Mediterranean diet score, and lung cancer: a prospective study. Cancer Causes Control. 2016; 27(7):907–17. Epub 2016/06/14. https://doi.org/10.1007/s10552-016-0770-1 PMID: 27294725; PubMed Central PMCID: PMC5550291.

34. Boden S, Wennberg M, Van Guelpen B, Johansson I, Lindahl B, Andersson J, et al. Dietary inflammatory index and risk of first myocardial infarction; a prospective population-based study. Nutr J. 2017; 16(1):21. Epub 2017/04/06. https://doi.org/10.1186/s12973-017-0243-8 PMID: 28376792; PubMed Central PMCID: PMCPMC5379659.

36. Lundyquist A, Andersson E, Ahlberg I, Nilbert M, Gerdtham U. Socioeconomic inequalities in breast cancer incidence and mortality in Europe—a systematic review and meta-analysis. Eur J Public Health. 2016; 26(5):804–13. Epub 2016/05/26. https://doi.org/10.1093/eurpub/ckw070 PMID: 27221607; PubMed Central PMCID: PMC5054273.

38. Pan P, Yu J, Wang LS. Diet and colon: what matters? Current opinion in gastroenterology. 2018. Epub 2018/12/15. https://doi.org/10.1097/mog.0000000000000501 PMID: 30550380.

40. Park YM, Zhang J, Steck SE, Fung TT, Hazlett LJ, Han K, et al. Obesity Mediates the Association between Mediterranean Diet Consumption and Insulin Resistance and Inflammation in US Adults. J Nutr. 2017. Epub 2017/03/17. https://doi.org/10.3945/jn.116.243543 PMID: 28298537.
41. Grosso G, Buscemi S, Galvano F, Mistretta A, Marventano S, La Vela V, et al. Mediterranean diet and cancer: epidemiological evidence and mechanism of selected aspects. BMC Surg. 2013; 13 Suppl 2: S14. Epub 2013/12/07. https://doi.org/10.1186/1471-2482-13-S2-S14 PMID: 24267672; PubMed Central PMCID: PMCPMC3850991.

42. Hebert JR, Ebbeling CB, Matthews CE, Hurley TG, Ma Y, Druker S, et al. Systematic errors in middle-aged women's estimates of energy intake: comparing three self-report measures to total energy expenditure from doubly labeled water. Ann Epidemiol. 2002; 12(8):577–86. Epub 2002/12/24. PMID: 12495831.

43. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. BMJ. 2008; 337:a1344. Epub 2008/09/13. https://doi.org/10.1136/bmj.a1344 PMID: 18786971; PubMed Central PMCID: PMCPMC2533524.

44. Pukkala E, Andersen A, Berglund G, Gislafoss R, Gudnason V, Hallmans G, et al. Nordic biological specimen banks as basis for studies of cancer causes and control—more than 2 million sample donors, 25 million person years and 100,000 prospective cancers. Acta Oncol. 2007; 46(3):286–307. Epub 2007/04/24. https://doi.org/10.1080/02841079700120554 PMID: 17450464.

45. Weinheil L, Hallgren CG, Westman G, Janlert U, Wall S. Reduction of selection bias in primary prevention of cardiovascular disease through involvement of primary health care. Scand J Prim Health Care. 1998; 16(3):171–6. Epub 1998/11/04. PMID: 9800231.