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ARTICLE

Epidemiology

Inflammatory potential of diet and colorectal carcinogenesis: a prospective longitudinal cohort

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BACKGROUND: Acknowledging the role of inflammation in colorectal carcinogenesis, this study aimed to evaluate the associations between diet-associated inflammation, as measured by the energy-adjusted dietary inflammatory index (E-DII™), and distinct stages of colorectal carcinogenesis.
METHODS: The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial enrolled participants without a colorectal cancer history, who were asked to complete baseline questionnaires and food frequency questionnaires. To estimate the associations between the E-DII and risks of newly incident colorectal adenoma, recurrent adenoma, and colorectal cancer, multivariable-adjusted Cox proportional hazards regression models were employed.
RESULTS: Among 101,680 participants, with an average age of 65 years, a total of 1177 incident colorectal adenoma cases, 895 recurrent adenoma cases and 1100 colorectal cancer cases were identified. Higher E-DII scores from food and supplement ($HR_{Q5\ vs\ Q1}$: 0.86 [0.69–1.06], P_{trend}: 0.27) or from food only ($HR_{Q5\ vs\ Q1}$: 0.82 [0.64–1.05], P_{trend}: 0.06) were not associated with higher risks of incident adenoma. However, the elevated risk of recurrent adenoma was found in the highest category of E-DII from food plus supplement ($HR_{Q5\ vs\ Q1}$: 1.63 [1.28–2.03], P_{trend}: < 0.001) when compared with the lowest category. A significant association between colorectal cancer risk and E-DII from food plus supplement ($HR_{Q5\ vs\ Q1}$: 1.34 [1.09–1.65], P_{trend}: 0.009) was found, where this association was only pronounced in distal colorectal cancer.
CONCLUSION: Higher E-DII scores from diet plus supplement but not from diet only were associated with a higher risk of recurrent adenoma and distal colorectal cancer. The role of nutrient supplements on cancer risk, especially when combined with diet, needs to be elucidated in future studies.

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BACKGROUND

Colorectal cancer (CRC) is a public health problem accounting for an increasing health burden in developed countries, including the UK [1]. It was the third most commonly diagnosed cancer and the second leading cause of cancer-related death in the UK [2]. Colorectal carcinogenesis involves the malignant transformation of adenomas [3, 4]. Apart from that ageing and family history of CRC were identified as risk factors of adenomas and CRC development in epidemiological studies [5–7], chronic inflammation plays an important role in the initiation, progression, and promotion of CRC. Dysregulated inflammatory components (e.g leukocytes, cytokines and complement components) not only result in sustained inflammatory cell proliferation, activated stroma but also lead to increased reactive oxygen species generation, DNA damage, and reduced DNA repair [8–10]. Furthermore, accumulating evidence substantiates the association between nutrition and inflammation [11–13], underlining the important role of diet in modulating inflammatory processes [14].

The Dietary Inflammatory Index (DII®) is a valid dietary scoring method developed specifically to estimate potential inflammatory of individuals' diets [15]. A higher DII score represents a more pro-inflammatory diet; conversely, a lower DII score indicates a more anti-inflammatory diet [15]. Two previous observational studies evaluated the relationship between DII and colorectal incident adenoma, but found inconsistent results. In it, a case–control study from Iran with 130 incident adenoma cases suggested higher DII scores related to increased risk of colorectal adenoma [16]; however, Haslam et al found that the relationship only exists in males based on data from a large prospective cohort study [17]. In addition, a pooled analysis of two trials reported insignificant association between DII and the risk of colorectal adenoma recurrence [18]. Compared to limited evidence regarding the associations between DII and colorectal incident adenoma or colorectal recurrent adenoma, several reports demonstrated that a pro-inflammatory diet measured by DII was related to increased risk of CRC [16, 19].

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Apart from dietary inflammation, there is growing evidence that diet might select the microbiota composition, namely regulating many beneficial or harmful effects of gut bacteria [20, 21]. Zhang et al. [22] identified that 24 CRC-related microbes and plasma inflammatory factors like C-reactive protein and soluble tumour necrosis factor II changed with the colorectal adenoma–carcinoma sequence, supporting the hypothesis that gut microbiome and inflammation may gradually promote the development of CRC by forming a microenvironment. Given the equivocal nature of the evidence and what we know on the association between inflammation and adenoma–carcinoma sequence from previous studies, it is conceivable that the inflammatory potential of diet might have differential effects at different stages of cancer progression.

We aimed to evaluate the potential effect of DII on different carcinogenesis stages (i.e. newly incident adenomas, recurrent adenomas, and CRC) using the longitudinal cohort from the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial.

METHODS

Study design and setting

Longitudinal data analysed in this study were obtained from the PLCO Cancer Screening Trial, a large-scale, prospective, multicenter randomised trial comparing screening tests and usual care to determine the effects of screening on mortalities related to prostate, lung, colorectal, and ovarian cancers. The study design of the trial had been described elsewhere [23]. Participants were enrolled according to these criteria: (i) had no history of prostate cancer, lung cancer, colorectal cancer, or ovarian cancer; (ii) were not participating in other cancer prevention or screening trial; (iii) were not receiving cancer treatment (excluding treatment for squamous and basal cell skin cancer); (iv) did not receive screening examinations for prostate cancer or colorectal cancer recently [23]. A total of 154,897 individuals aged 55–74 years were recruited from November 1993 to July 2001 across ten screening centres in the USA. Participants were divided into the intervention arm who receiving flexible 60-cm sigmoidoscopy (FSG) and the control arm with usual care. FSG was performed at study entry (T_0), and then at the 3-(T_3) or 5-(T_5) year follow-up for participants in the intervention arm [24, 25]. If these screens were suspicious for colorectal cancer, endoscopic follow-up (colonoscopy) was anticipated. Supplementary Fig. 1 displayed the study flowchart for identifying eligible participants in PLCO trial.

For this study, we further excluded participants if they were (i) without Baseline Questionnaire completion; (ii) without valid Diet History Questionnaires (DHQ) or Diet Questionnaire (DQX) (the valid DHQ/DQX refers to DHQ/DQX with the date of DHQ/DQX completion, the date of DHQ/DQX completion prior to the date of death, no more than 8 missing items, and no extreme values of energy intake); (iii) with colorectal cancer diagnosis before DHQ/DQX completion.

Data collection

At the entry of the trial, participants were asked to complete a Baseline Questionnaire, including age, gender, race, marital status, education level, smoking status, body mass index (BMI = weight (kg)/height $(m)^2$), family history of colorectal cancer and history of diabetes. Other data including physical activity, family income and non-steroidal anti-inflammatory drugs (NSAID) use status were collected by the Supplemental Questionnaires. To capture nutrient data including energy intake and alcohol drinking status, the DHQ/DQX was used. The DHQ is a food frequency questionnaire that contains 124-item food and supplement use, which was released in 1998 and introduced 5 years in both arms of the PLCO trial. Participants reported frequency and portion size of dietary intake and supplement use over the past year [26]. Likewise, the DQX, a 137-item food frequency questionnaire, was administered at baseline to the participants in the intervention arm only [27].

Energy-adjusted dietary inflammatory index calculation

Details regarding development of DII were described extensively elsewhere [15]. Briefly, the DII derives from literature, and was designed to estimate the overall potential inflammatory of diet. A total of 1943 studies published through 2010 were identified and scored to produce the component-specific inflammatory effect scores for 45 food parameters. These food parameters are consisting of micronutrients, macronutrients, some bioactive components, and these parameters are related to inflammatory biomarkers such as tumour necrosis factor-α, C-reactive protein, interleukin (IL) -10, IL-6, IL-4 and IL-1β. The scoring algorithm of DII was constructed based on the effect of food parameter on inflammation. More specifically, "+1" was assigned if the food parameter significantly increased the aforementioned inflammatory biomarkers (namely the effects were pro-inflammatory); "−1" was assigned if the effects were anti-inflammatory; and "0" was assigned if the food parameter had no significant effect on these inflammatory biomarkers. The score for each article was weighted by study design (study design weights: 10 for experimental study in humans, 8 for the prospective cohort study, 7 for case–control study, 6 for cross-sectional study, 5 for experiment study in animals and 3 for experimental study in cells), and food parameter-specific inflammatory effect scores were obtained based on these weighted values. The score can have values ranging from 7.98 (the maximally pro-inflammatory diet score) to −8.87 (the maximally anti-inflammatory diet score) in seven scenarios [15]. Supplementary Fig. 2 presented the steps of DII calculation.

To avoid the arbitrariness caused by simply using raw intake amounts, dietary data in the DHQ/DQX were standardised to a composite dietary database that was established based on 11 datasets deriving from various populations globally. Food and nutrient consumption were adjusted for total energy per 1000 calories, and the energy-adjusted nutrient data was used to calculate energy-adjusted DII (E-DII^{TM}). Except for ten DII components including ginger, turmeric, garlic, oregano, rosemary, eugenol, saffron, flavonols, n-3 fatty acids and n-6 fatty acids, the remaining 35 components (alcohol, caffeine, carbohydrate, cholesterol, energy, total fat, fibre, folic acid, monounsaturated fatty acids, polyunsaturated fatty acids, saturated fat, trans fat, onion, protein, green/black tea, anthocyanidins, pepper, flavan-3-ol, flavones, flavonones, isoflavones, vitamin A, vitamin C, vitamin D, vitamin B12, vitamin B6, riboflavin, thiamin, niacin, vitamin E, β-Carotene, iron, magnesium, selenium, zinc) were acquired for E-DII calculation based on DHQ/DQX in this study. Considering that most participants in the PLCO Cancer Screening Trial consumed nutrient supplement, we used the E-DII score from food and supplement and from food only separately for analyses. Available nutrient supplements, including vitamin A, vitamin C, vitamin D, vitamin B12, vitamin B6, riboflavin, thiamin, niacin, vitamin E, β-Carotene, iron, magnesium, selenium, and zinc, were employed to calculate E-DII from food and supplement.

Outcome ascertainment

Colorectal incident adenoma. Participants with a negative FSG screen at T_0 were eligible for the evaluation of colorectal incident adenoma risk. We identified an incident adenoma case or control according to FSG screen at T_3 or T_5: cases were defined as participants with the discovery of a left-sided adenoma at T_3 or T_5 screens [25]; controls were defined as those have a negative T_3 or T_5 FSG screens. An adenoma with high-grade dysplasia or villous component, more than 1 cm in size was considered as an advanced adenoma.

Recurrent colorectal adenoma. Data of the recurrent adenoma cohort derived from the subset of PLCO cohort—the Study of Colonoscopy Utilization (SCU) (https://cdas.cancer.gov/learn/plco/scu/). Participants who had a positive T_0 FSG screen at baseline and had an adenoma found as a result of that screen were eligible to be included in the recurrent adenoma cohort. An adenoma found within the first 18 months following the positive T_0 FSG screen was defined as a baseline adenoma, on the first endoscopy that followed the T_0 FSG screen, or on an endoscopy within 6 months from the first endoscopy following the screen [25]. In this sub-study, individuals diagnosed as adenoma at subsequent screens (T3/5) were defined as recurrent colorectal adenoma cases, while participants with a positive baseline adenoma but free of adenoma at screens were considered as participants without a recurrent adenoma.

Colorectal cancer incidence. After enrollment during November 1993 and July 2001, participants received screening exams at T_3 and T_5. Letters were mailed to participants and their health care providers usually within 3 weeks of an exam. Participants who had a self-report CRC or who had received a positive screening result were encouraged to receive a diagnostic evaluation. The diagnosis of colorectal cancer was ascertained

by an annual study update form, and medical records were abstracted and reviewed. Participants diagnosed with colorectal cancer were extracted according to the International Classification of Diseases for Oncology, Third Edition (ICD-O-3), which was coded as C180-C189, C199, C209, and C260). Data were collected on cancer diagnoses that occurred through December 31, 2009.

Statistical analysis

Participants were divided into tertiles or quintiles according to the distribution of E-DII scores. The primary analysis was conducted within E-DII quintiles, while subgroup analysis employed E-DII tertiles due to smaller sample sizes. Characteristics of participants were described by mean with standard deviation for continuous variables that normally distributed and median with interquartile range (IQR) were employed for the presentation of non-normally distributed continuous variables. For categorical variables, frequencies with composition ratio were calculated.

Cox proportional hazards regression was employed to calculate multivariable-adjusted hazards ratio (HR) with 95% confidence intervals (95% CI) for the association between risk of incident or recurrent colorectal adenoma and E-DII derived from DQX. Time to incident adenoma or recurrent adenoma event was defined as years from DQX completion until adenomas found, and censoring time for the two endpoints was defined as DQX completion to the date of last colonoscopy, colorectal cancer diagnosis, or death, whichever occurred first. Given the latency from colorectal adenoma to CRC, we excluded possibly "synchronous" CRC cases that developed 3 years from baseline. Cases with adenoma and CRC were also removed. After exclusion, the remained cases were employed for analysis. CRC risk was also estimated using HR with 95% CI from multivariable-adjusted Cox proportional hazards models. Time to CRC incidence was defined as years from DHQ completion until CRC diagnosis, and censoring time for incident CRC event was defined as DHQ completion to death, other cancers diagnosis, or last contact. Linear trends across quintiles of E-DII were examined by median value of each quintile, which was regarded as a continuous variable in the Cox proportional hazards regression models. Confounding factors selection was based on biological plausibility, literature reports and/or ≥10% change in relative risks [28] of both E-DII (in either continuous or categorical format) and colorectal adenoma/cancer. The proportional hazards assumption was examined using the Schoenfeld residual test [29]. There was no evidence that E-DII or any covariate violated the proportional hazards assumption.

Effect modification by co-variables was examined by adding the cross-product of each effect modifier with E-DII quintiles in the multivariable-adjusted model. Considering the reduction of sample size after stratification, we divided participants into tertiles in subgroup analyses. Clinically relevant co-variables including age (≤65 years, >60 years) and family history of colorectal cancer (no family history of colorectal cancer, has a family history of colorectal cancer) were considered as potential effect modifiers. To further assess the significance of sub-endpoints, advanced adenomas and location specific-CRC (i.e. distal and proximal tumours) were extracted from the above main analyses. In addition, to assess the stability of the main results, we also repeated the main analyses using E-DII tertiles.

All statistical analyses were conducted by R software (version 3.6.2). The statistical significance level was set at $P < 0.05$ (two-sided).

RESULTS

Participant characteristics

Table 1 displayed the baseline characteristics of study participants from the intervention arm. E-DII scores (calculated by the DQX) from food and supplement were divided into 5 groups: Q1 (−7.10, −2.44), Q2 (−2.43, −0.88), Q3 (−0.87, 0.57), Q4 (0.58, 2.26), Q5 (2.27, 7.27), while E-DII scores from food shared the magnitude between −7.52 to 7.42 [Q1 (−7.52, −2.64, Q2 (−2.63, −0.92), Q3 (−0.91, 0.66), Q4 (0.67, 2.49), Q5 (2.50, 7.42)]. Compared to participants with the lowest E-DII scores from food and supplement, participants whose diet was more pro-inflammatory were more likely to be male, current smoker, have higher BMI, higher energy intake, inferior education level, and have less physical activity. As for E-DII calculated by food only categories, participants with more pro-inflammatory diet that indicated by the highest E-DII scores derived from diet only seem to be male, have higher energy intake, have lower education level, have less exercise. In Supplement Table 1, participants' characteristics in the whole trial (both arms) were presented. Based on DHQ, the groups of E-DII scores from food and supplement were: Q1 (−8.63, −5.66), Q2 (−5.65, −4.64), Q3 (−4.63, −3.43), Q4 (−3.42, −1.64), Q5 (−1.63, 5.81), and the range of scores from food only was from −7.77 to 6.17 [Q1 (−7.77, −4.16)), Q2 (−4.15, −2.96), Q3 (−2.95, −1.67), Q4 (−1.66, −0.04), Q5 (−0.03, 6.17)]. Compared to those in the lowest category, participants with the highest E-DII calculated by food plus supplements or by food only tended to be male, current smoker, have higher energy intake, higher BMI, lower education level and less physical activity.

Supplementary Table 2 presented the correlations of the E-DII between the two diet assessment instrument (E-DII from food and supplement, $r = 0.49$; E-DII from food only, $r = 0.38$) and within each dietary questionnaire, correlations between E-DII from food only and E-DII from food and supplement (DHQ, $r = 0.84$; DQX, $r = 0.84$).

Incident colorectal adenoma

A total of 1177 cases among 61,279 participants were identified. The highest quintile of E-DII from both diet and supplement was not significantly associated with the risk of incident adenoma with a multivariable-adjusted HR of 0.86 (95% CI: 0.69-1.06, $P_{trend} = 0.27$). In a subgroup analysis, the association between incident advanced adenoma and E-DII was found to be nonsignificant (multivariable-adjusted HR: 1.29, 95% CI: 0.83–2.01; $P_{trend} = 0.35$). The risks of incident adenoma or incident advanced adenoma from E-DII derived from food only were comparable with that of E-DII derived from both food and supplement (Table 2). The results were consistent when stratifying participants with a family history of CRC (Table 3).

Recurrent adenoma

A total of 895 recurrent adenoma cases were identified. A significant association between E-DII from food and supplement and elevated risk of recurrent adenoma was found (multivariable-adjusted $HR_{Q5\ vs\ Q1}$: 1.63, 95% CI: 1.28–2.03, $P_{trend} < 0.001$). On the risk of recurrent advanced adenoma, the association was found to be stronger (E-DII from food and supplement, multivariable-adjusted $HR_{Q5\ vs\ Q1}$: 1.68, 95% CI: 1.05–2.63, $P_{trend} = 0.03$). When repeating analyses using E-DII from food only, the increased risk of recurrent adenoma (multivariable-adjusted $HR_{Q5\ vs\ Q1}$: 1.16, 95% CI: 0.90–1.53, $P_{trend} = 0.46$) or advanced recurrent adenoma (multivariable-adjusted $HR_{Q5\ vs\ Q1}$: 0.95, 95% CI: 0.53–1.66, $P_{trend} = 0.96$) disappeared (Table 2).

We failed to find interaction effect of family history of CRC on the association between E-DII from food and supplement and the risk of colorectal recurrent adenoma ($P_{interaction}$: 0.66) (Table 3).

Colorectal cancer incidence

During an average follow-up of 9.4 years, 1100 CRC cases were identified in total. After excluding CRC cases that diagnosed 3 years from baseline and cases with adenoma, a total of 1022 CRC cases were employed in the primary analytic approach. According to the results of multivariable-adjusted Cox proportional hazards regressions, higher E-DII score from food and supplement was significantly related to an increased risk of CRC ($HR_{Q5\ vs\ Q1}$: 1.34, 95% CI: 1.09–1.65; $P_{trend} = 0.009$). When stratifying CRC using tumour location, we found statistically significant associations between E-DII and distal CRC incidence, and the associations were no different when analyses were broken down by the calculation of E-DII (E-DII from food and supplement: multivariable-adjusted $HR_{Q5\ vs\ Q1}$: 1.79, 95% CI: 1.28–2.48; $P_{trend} < 0.001$; E-DII from food: multivariable-adjusted $HR_{Q5\ vs\ Q1}$: 1.43, 95% CI: 1.04–1.97; $P_{trend} = 0.006$). By contrast, we did not observe any significant associations in proximal CRC, P_{trend} for E-DII from food and supplement was 0.69 and P_{trend} for E-DII from food was 0.41 (Table 2). In addition, the results showed a slight difference when stratifying by age. Participants in pro-inflammatory diet who were less than 65 years

Table 1. Baseline characteristics of study participants in the intervention arm by quintiles of energy-adjusted dietary inflammatory index (E-DII), Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial, 1991 to 2009.

	E-DII from diet and supplement		**E-DII from diet only**	
	Q1 (−7.10, −2.44) (*N* = 12,259)	**Q5 (2.27, 7.27) (*N* = 12,259)**	**Q1 (−7.52, −2.64) (*N* = 12,259)**	**Q5 (2.50, 7.42) (*N* = 12,259)**
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**
Age at DQX, years	62 (58, 67)	62 (58, 66)	63 (59, 67)	62 (58, 66)
Body mass index (kg/m^2)	25.8 (23.5, 29.2)	27.0 (24.3, 30.2)	26.5 (23.9, 29.4)	26.6 (24.0, 30.1)
Energy intake, kcal/day	1471.7 (1149.2, 1860.0)	2386.0 (1906.2, 3035.2)	1304.6 (1048.0, 1611.8)	2686.3 (2217.2, 3292.5)
	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**
Gender				
Male	6055 (49.4)	6371 (52.0)	4945 (40.3)	7085 (57.8)
Female	6201 (50.6)	5885 (48.0)	7314 (59.7)	5174 (42.2)
Race/ethnicity				
White, non-Hispanic	10,963 (89.5)	11,075 (90.4)	10,971 (89.5)	11,073 (90.3)
Black, non-Hispanic	379 (3.1)	678 (5.5)	423 (3.5)	680 (5.5)
Hispanic	181 (1.5)	209 (1.7)	183 (1.5)	217 (1.8)
Asian	636 (5.2)	217 (1.8)	585 (4.8)	219 (1.8)
Other[a]	93 (0.8)	73 (0.6)	93 (0.8)	68 (0.6)
Unknown	4 (0.0)	4 (0.0)	4 (0.0)	2 (0.0)
Marital status				
Never married	437 (3.6)	384 (3.1)	425 (3.5)	379 (3.1)
Married or living as married	9445 (77.1)	9477 (77.3)	9738 (79.4)	9020 (73.6)
Divorced or separated	1355 (11.1)	1352 (11.0)	1184 (9.7)	1625 (13.3)
Widowed	1006 (8.2)	1037 (8.5)	897 (7.3)	1226 (10.0)
Unknown	13 (0.1)	6 (0.0)	15 (0.1)	9 (0.1)
Education level				
Less than high school	546 (4.5)	1258 (10.3)	638 (5.2)	1182 (9.6)
High school graduate or equivalent	1946 (15.9)	3767 (30.7)	2015 (16.4)	3737 (30.5)
Post-high school education	1436 (11.7)	1696 (13.8)	1426 (11.6)	1678 (13.7)
College education or higher	8316 (67.9)	5523 (45.1)	8167 (66.6)	5650 (46.1)
Unknown	12 (0.1)	12 (0.1)	13 (0.1)	12 (0.1)
Physical activity				
Active less than one time per month	606 (4.9)	1224 (10.0)	568 (4.6)	1279 (10.4)
Active at least one time per month	7895 (64.4)	6560 (53.5)	7762 (63.3)	6568 (53.6)
Unknown	3755 (30.6)	4472 (36.5)	3929 (32.0)	4412 (36.0)
Smoking status				
Never smoked	5951 (48.6)	5436 (44.4)	5985 (48.8)	5526 (45.1)
Former smoker	5505 (44.9)	5041 (41.1)	5459 (44.5)	4928 (40.2)
Current smoker	798 (6.5)	1778 (14.5)	813 (6.6)	1801 (14.7)
Unknown	2 (0.0)	1 (0.0)	2 (0.0)	4 (0.0)
Alcohol drinking status				
Non-drinker	2172 (17.7)	3623 (29.4)	2037 (16.6)	3772 (30.8)
Drinker	10,084 (82.3)	8633 (70.4)	10,222 (83.4)	8487 (69.2)
Family history of colorectal cancer				
No	10,688 (87.2)	10,453 (85.3)	10,658 (86.9)	10,467 (85.4)
Yes	1207 (9.8)	1269 (10.4)	1218 (9.9)	1293 (10.5)
Possible	276 (2.3)	444 (3.6)	291 (2.4)	410 (3.3)
Unknown	85 (0.7)	90 (0.7)	92 (0.8)	89 (0.7)
History of diabetes				
No	11,366 (92.7)	11,328 (92.4)	11,228 (91.6)	11,431 (93.2)

Table 1. continued

	E-DII from diet and supplement		E-DII from diet only	
	Q1 (−7.10, −2.44) (*N* = 12,259) Median (IQR)	Q5 (2.27, 7.27) (*N* = 12,259) Median (IQR)	Q1 (−7.52, −2.64) (*N* = 12,259) Median (IQR)	Q5 (2.50, 7.42) (*N* = 12,259) Median (IQR)
Yes	848 (6.9)	886 (7.2)	990 (8.1)	788 (6.4)
Unknown	42 (0.3)	42 (0.3)	41 (0.3)	40 (0.3)
NSAIDs user				
No	4818 (39.3)	5064 (41.3)	5036 (41.1)	4815 (39.3)
Yes	4058 (33.1)	3304 (27.0)	3689 (30.1)	3604 (29.4)
Unknown	3380 (27.6)	3888 (31.7)	3534 (28.8)	3840 (31.3)

E-DII Energy-Adjusted Dietary Inflammatory Index, *DHQ* Diet History Questionnaire, *NSAIDs* non-steroidal anti-inflammatory drugs.
[a]Other race, including Pacific Islander and American Indian.
The E-DII was calculated based on the DQX.

Table 2. Multivariable-adjusted[a] associations between energy-adjusted dietary inflammatory index (E-DII) and colorectal incident adenoma, recurrent adenoma, and colorectal cancer[b], Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial, 1991 to 2009.

	Cases	E-DII quintiles					P_{trend}[c]
		Q1	Q2	Q3	Q4	Q5	
Any adenoma							
E-DII from food and supplement	1177	Reference	0.80 (0.66, 0.97)	0.95 (0.79, 1.16)	0.82 (0.67, 1.00)	0.86 (0.69, 1.06)	0.27
E-DII from food only	1177	Reference	0.87 (0.72, 1.04)	0.77 (0.63, 0.94)	0.75 (0.60, 0.94)	0.82 (0.64, 1.05)	0.06
Advanced adenoma							
E-DII from food and supplement	279	Reference	0.95 (0.64, 1.40)	1.19 (0.79, 1.78)	0.93 (0.61, 1.42)	1.29 (0.83, 2.01)	0.35
E-DII from food only	279	Reference	1.50 (1.02, 2.20)	0.94 (0.61, 1.45)	1.03 (0.64, 1.66)	1.30 (0.77, 2.18)	0.95
Any recurrent adenoma							
E-DII from food and supplement	895	Reference	1.08 (0.86, 1.32)	1.23 (0.99, 1.53)	1.16 (0.92, 1.42)	1.63 (1.28, 2.03)	<0.001
E-DII from food only	895	Reference	1.25 (1.03, 1.56)	1.12 (0.90, 1.42)	1.23 (0.96, 1.57)	1.16 (0.90, 1.53)	0.46
Advanced recurrent adenoma							
E-DII from food and supplement	229	Reference	1.10 (0.72, 1.69)	1.06 (0.67, 1.65)	1.08 (0.70, 1.73)	1.68 (1.05, 2.63)	0.03
E-DII from food only	229	Reference	1.20 (0.76, 1.79)	1.10 (0.69, 1.72)	1.27 (0.80, 2.03)	0.95 (0.53, 1.66)	0.96
Colorectal cancer							
E-DII from food and supplement	1022	Reference	1.21 (0.99, 1.48)	1.10 (0.89, 1.35)	1.26 (1.03, 1.55)	1.34 (1.09, 1.65)	0.009
E-DII from food only	1022	Reference	0.93 (0.76, 1.13)	1.07 (0.88, 1.30)	1.14 (0.94, 1.38)	1.06 (0.86, 1.30)	0.17
Proximal colorectal cancer							
E-DII from food and supplement	601	Reference	1.02 (0.79, 1.33)	0.89 (0.67, 1.17)	1.22 (0.93, 1.61)	0.99 (0.75, 1.29)	0.69
E-DII from food only	601	Reference	0.91 (0.70, 1.18)	1.08 (0.83, 1.41)	1.03 (0.79, 1.33)	1.07 (0.81, 1.42)	0.41
Distal colorectal cancer							
E-DII from food and supplement	421	Reference	1.34 (0.97, 1.88)	1.39 (1.00, 1.94)	1.65 (1.19, 2.28)	1.79 (1.28, 2.48)	<0.001
E-DII from food only	421	Reference	1.05 (0.76, 1.49)	1.38 (1.01, 1.90)	1.44 (1.05, 1.97)	1.43 (1.04, 1.97)	0.006

E-DII Energy-Adjusted Dietary Inflammatory Index, *NSAIDs* non-steroidal anti-inflammatory drugs.
[a]Adjusted for age (continuous), energy intake (continuous), gender (male, female), body mass index (continuous), smoking status (current, former, never), alcohol drinking status (current, former, never), marital status (single, married, divorced or separated, widowed), educational level (less than high school, high school graduate or equivalent, post-high school education, college education or higher), physical activity (active less than one time per month, active at least one time per month), family history of colorectal cancer (yes, no) and NSAIDs use status (yes, no). Multivariable-adjusted Cox hazards regressions for colorectal cancer further adjusted trial arm (intervention group, control group).
[b]DQX was used to calculate E-DII scores for analyses on incident adenoma and recurrent adenoma, DHQ was employed for E-DII calculation on analyses of colorectal cancer.
[c]Linear trends across quintiles of E-DII scores were tested by modelling the median value in each quintile as a continuous variable in Cox regression.

old had 39% higher risk to develop CRC than their elder counterpart (>65 years) (Table 3).

DISCUSSION

The study was conducted to assess whether an anti-inflammatory diet influences colorectal carcinogenesis, and at which stage in the process is the association most evident. We found a higher E-DII score from diet plus supplement is associated with a higher risk of adenoma recurrence, as well as CRC and this positive association was only prominent in distal CRC rather than proximal CRC.

Previous studies [16, 17] found that the most inflammatory group of E-DII scores had increased risk of colorectal adenoma

Table 3. Risk of colorectal adenomas and cancer incidence from E-DII from food and supplement stratified by family history of colorectal cancer and age.

	E-DII Tertiles[a]			$P_{interaction}$[d]
	T1	T2	T3	
Incident adenoma				
No family history of colorectal cancer (N)	340	339	346	0.32
Multivariable-adjusted HR (95% CI)[b]	Reference	0.97 (0.83, 1.13)	0.95 (0.79, 1.13)	
Have a family history of colorectal cancer (N)	38	38	45	
Multivariable-adjusted HR (95% CI)[b]	Reference	0.62 (0.37, 1.04)	0.80 (0.46, 1.39)	
Recurrent adenoma				
No family history of colorectal cancer (N)	202	254	278	0.66
Multivariable-adjusted HR (95% CI)[b]	Reference	1.11 (0.92, 1.35)	1.05 (0.85, 1.30)	
Have a family history of colorectal cancer (N)	34	37	43	
Multivariable-adjusted HR (95% CI)[b]	Reference	1.22 (0.74, 1.99)	0.99 (0.58, 1.68)	
Colorectal cancer				
Age ≤65, years	130	154	180	0.16
Multivariable-adjusted HR (95% CI)[c]	Reference	1.11 (0.85, 1.45)	1.59 (1.21, 2.08)	
Age >65, years	114	116	127	
Multivariable-adjusted HR (95% CI)[c]	Reference	1.09 (0.67, 1.20)	1.20 (0.99, 1.45)	

[a]The E-DII tertiles are as follows: for analyses on incident adenoma and recurrent adenoma, T1: −7.10 to −1.37, T2: −1.36 to 1.10, T3: 1.11 to 7.27; for analysis on colorectal cancer, T1: −8.63 to −5.00, T2: −4.99 to −2.92, T3: −2.91 to 5.81.
[b]Adjusted for age (continuous), gender (male, female), body mass index (continuous), smoking status (current, former, never), alcohol drinking status (current, former, never), marital status (single, married, divorced or separated, widowed), educational level (less than high school, high school graduate or equivalent, post-high school education, college education or higher), physical activity (active less than one time per month, active at least one time per month), and Non-steroidal anti-inflammatory drugs use status (yes, no).
[c]Adjusted for gender (male, female), body mass index (continuous), smoking status (current, former, never), alcohol drinking status (current, former, never), marital status (single, married, divorced or separated, widowed), educational level (less than high school, high school graduate or equivalent, post-high school education, college education or higher), physical activity (active less than one time per month, active at least one time per month), family history of colorectal cancer (yes, no), and non-steroidal anti-inflammatory drugs use status (yes, no).
[d]$P_{interaction}$ was calculated by adding the cross-product of quintile E-DII in the multivariable-adjusted Cox regression model.

compared to those with more anti-inflammatory diet. Although both Haslam et al [17] and the current study used the data from PLCO trial, this study included extended follow-up data (1991–2010) rather than those (1991–2000) used by Haslam et al. Haslam et al revealed a positive relationship between colorectal incident adenoma risk and inflammatory diet that indicated by DHQ-derived E-DII. Considering that the introduction of DHQ and screening is synchronous, the cross-sectional design lacks validity to present the association. This study further examined the association using cohort with prospectively collected DQX, which was confirmed by a colonoscopy screening-based cross-sectional study [30]. Based on the prospective study design, we did not observe any association between future development of incident adenoma and baseline E-DII calculated from food plus supplements or from food only. Considering the heterogeneity of the results and potential biases in cross-sectional study design, findings from this study further added new evidence.

Our findings also support that a more pro-inflammatory diet may had an effect on increased risk of colorectal adenoma recurrence, while this association only exist when calculating E-DII by food and supplement. By contrast, a pooled analysis of Wheat Bran Fibre (WBF) and Ursodeoxycholic Acid (UDCA) clinical trials found no association between DII and odds of recurrent colorectal adenoma [18]. Although the results from the pooled analysis were inconsistent with this study, in our view, it could be argued that there was a potential positive relationship between E-DII score and risk of colorectal adenoma recurrence. On one side, the E-DII score range (−7.0 to 3.3) of the pooled analysis is much smaller than that of this study (−7.10 to 7.27), indicating lower proportions of both more anti-inflammatory and more pro-inflammatory diet. On the other hand, it seems some patients relapsed with advanced adenoma or subsequent CRC instead of recurrent adenoma, which is confirmed by the much higher risk of advanced recurrent adenoma we observed. We observed a higher risk to develop CRC in pro-inflammatory diet when completely removing cases with adenoma history from CRC analyses [entire CRC cases: HR with 95% CI for E-DII from food and supplement is 1.29 (1.06, 1.57); CRC cases diagnosed over 3 years from baseline: HR with 95% CI for E-DII from food and supplement is 1.34 (1.09, 1.65)], which somewhat supported the point of view above. It is reasonable to suggest that patients with a history of colorectal adenoma could incorporate anti-inflammatory diet patterns to help prevent advanced recurrent adenoma or even CRC.

The literatures regarding the association between E-DII/DII and risk of CRC were basically consistent. Results from previous studies based on various population suggested a pro-inflammatory diet was associated with increased CRC risk [31–36]. This study further found that the increased risk was stronger for E-DII from food and supplement than E-DII from food only, which questioned the role of dietary supplements in the process of CRC carcinogenesis. Dietary supplements are widely used, and at least one supplement use in the past month was reported in half of US adults, where the most common used dietary supplements are multivitamin and multimineral, vitamin, and mineral supplements [37]. Adequate intake of these micronutrients is required to maintain optimal health, but the possibility of toxicity increases with increasing dose [38], largely due to that dietary micronutrient deficiency is increasingly rare in developed countries, most supplement consumers actually have excess vitamin and mineral intake [39]. Among available DII calculation components, iron and vitamin B12 were pro-inflammation surrogators. Excess consumption of iron

(supplemental intake more than 18 mg per day) could lead to a 130% higher risk of CRC [40]. A multicenter RCT observed that B vitamins (folic acid and vitamin B12) were also significantly associated with a higher risk of CRC [41]. Although other available supplements in DII calculation are anti-inflammation, many are fat-soluble vitamins. Reports of toxicity associated with overconsumption of these vitamins were more prevalent. Previous studies indicated that vitamin E supplementation following radiation therapy increased cancer recurrence for head and neck cancer patients [42], two trials found that male smokers receiving β-carotene supplements had significantly increased risk of lung cancer [43, 44].

Besides, there are great differences regarding the protective effect of anti-inflammatory diets on different tumour location. The different protective effects observed between proximal CRC and distal CRC might attribute to differences in bacterial population on the two sides of intestinal tract, or exposure to distinct nutrients and bile acids [45]. Previous studies suggested the pro-inflammatory diet was associated with a higher risk of developing colon cancer [46] or proximal colon cancer [47]. Recent studies tended to indicate such association exist in both colon and rectal cancer, but is much prominent for rectal cancer [31] or distal CRC [36]. We observed a significant association between E-DII and distal CRC incidence rather than proximal tumours, which may be explained by more frequent FSG in the PLCO cancer screening trial. It is easier to detect distal CRC than proximal CRC in the early stages since distal CRC have polypoid morphology of distal CRC [48, 49]. Nevertheless, it is still valuable to recommend anti-inflammatory diet, especially for younger individuals who are at a higher risk of distal CRC [50].

Potential mechanisms illustrated that diet is an important factor in the process of carcinogenesis. First, pro-inflammatory diets have effects on insulin resistance by increasing systemic inflammation [51]. Second, diet plays a role of local inflammation and oxidation, which leads to focal proliferation and mutagenesis [52]. Third, antioxidant components contained in some low E-DII scores foods like fruits, vegetables, coffee, tea, etc. could exert its function on anti-inflammatory through the action of local microbiota [53]. Fourth, consumption of red and processed meat that are high E-DII score foods increases levels of the haem iron content [54], N-nitroso compounds formed during the meat processing [55], and polycyclic aromatic hydrocarbons and heterocyclic aromatic amines from cooking meat at high temperatures, which results in hyperplasia [56]. Overall, diet-chronic inflammation is a persistent condition that tissue destruction and repair occur simultaneously [9]. It is evident that loss of control over normal tissue repair or renewal mechanisms may result in malignant transformation [57].

CRC is considered to arise from adenomas through the adenoma–carcinoma sequence. However, the results in this study are not consistent between E-DII to colorectal adenoma and CRC. Such findings support a hypothesis that the trajectory of the role of inflammation in 5–10 years of adenoma–carcinoma sequence might be a "J" shape, where many chromosomal rearrangements are acquired together in the short bursts of genomic instability early in tumour evolution [58, 59].

To our knowledge, no previous study has longitudinally and systematically evaluated the associations between E-DII and incident colorectal adenoma, recurrent adenoma, and incident cancer in the same cohort, which minimises misclassification that could occur when combining different studies. Besides, incorporating with this prospective cohort design, a standardised dietary assessment was conducted by a food frequency questionnaire that contained most major foods and nutrients consumed. The dietary information was collected by mail that accompanied by a cover letter and a postage-paid return envelope. For participants who did not return their questionnaires within 3 weeks, up to five telephone calls were made. Previous study reported that response rates for controls and screening arms are 81.9% and 84%, and the proportion of missing or uninterpretable is small (frequency of intake: 1.4% and 1.7%; portion size: 1.7% and 2.0%; use of dietary supplements: 6.0% and 5.4%) [27]. Finally, the PLCO cancer screening trial collected data from ten screening centres across the USA, thus the study population is highly representative. This study also has several limitations. First, this study has some potential selective bias. We excluded participants that has more than 8 missing DHQ/DQX items, which might lead to a "healthy participant effect", reporting lower incidence rates among participants who are interested in healthy lifestyles and more likely to take part in the prospective study. Participants with extreme energy intake (defined as the sex-specific first and last percentile of total energy) were also excluded, thus, the findings in this study should be interpreted carefully to individuals with a similar energy intake range. Second, the PLCO is a cancer screening trial, which examines only the distal colorectal region. This study was more likely to detect incident lesions from the left side, although recurrent adenoma and incident CRC cases included from both sides. However, there is a previous study that found FSG screening significantly reduced both proximal and distal CRC incidence in the PLCO [24]. Third, only 35 out of 45 food parameters were employed for E-DII calculation in this study, the remaining 10 food parameters are unavailable in the DHQ/DQX, which could lead to the reduction of predictability of E-DII. But a previous study indicated that the predictive capability of DII/E-DII is stable when the number of food parameters for DII calculation dropped from 44 to 27 [60].

In conclusion, findings from our study suggest that higher E-DII scores from diet plus supplement rather than from diet only, were associated with a higher risk of recurrent adenoma and distal colorectal cancer. Further studies on the role of nutrient supplements on cancer risk, especially when combined with diet, are needed.

DATA AVAILABILITY

Clinical and supplemental data that support the findings of this study have been deposited at https://biometry.nci.nih.gov/cdas/plco/. The PLCO trial has the following five registration numbers: NCT00002540 (Prostate), NCT01696968 (Lung), NCT01696981 (Colorectal), NCT01696994 (Ovarian) and NCT00339495 (EEMS) on ClinicalTrials.gov. This study had registered in Cancer Data Access System and had been approved.

REFERENCES

1. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385:117–71.
2. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. Eur J Cancer. 2010;46:765–81.
3. Strum WB. Colorectal adenomas. N. Engl J Med. 2016;374:1065–75.
4. Bedenne L, Faivre J, Boutron MC, Piard F, Cauvin JM, Hillon P. Adenoma—carcinoma sequence or "de novo" carcinogenesis? A study of adenomatous remnants in a population-based series of large bowel cancers. Cancer. 1992;69:883–8.
5. Brenner H, Kloor M, Pox CP. Colorectal cancer. Lancet. 2014;383:1490–502.
6. Kim SE, Paik HY, Yoon H, Lee JE, Kim N, Sung MK. Sex- and gender-specific disparities in colorectal cancer risk. World J Gastroenterol. 2015;21:5167–75.
7. Taylor DP, Burt RW, Williams MS, Haug PJ, Cannon-Albright LA. Population-based family history-specific risks for colorectal cancer: a constellation approach. Gastroenterology. 2010;138:877–85.
8. Lasry A, Zinger A, Ben-Neriah Y. Inflammatory networks underlying colorectal cancer. Nat Immunol. 2016;17:230–40.
9. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420:860–7.
10. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010;140:883–99.
11. Santos S, Oliveira A, Lopes C. Systematic review of saturated fatty acids on inflammation and circulating levels of adipokines. Nutr Res. 2013;33:687–95.
12. Bordoni A, Danesi F, Dardevet D, Dupont D, Fernandez AS, Gille D, et al. Dairy products and inflammation: a review of the clinical evidence. Crit Rev food Sci Nutr. 2017;57:2497–525.

13. Barbaresko J, Koch M, Schulze MB, Nöthlings U. Dietary pattern analysis and biomarkers of low-grade inflammation: a systematic literature review. Nutr Rev. 2013;71:511–27.
14. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444:860–7.
15. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. Public health Nutr. 2014;17:1689–96.
16. Rafiee P, Shivappa N, Hébert JR, Nasab SJ, Bahrami A, Hekmatdoost A, et al. Dietary inflammatory index and odds of colorectal cancer and colorectal adenomatous polyps in a case-control study from Iran. Nutrients. 2019;11:1213.
17. Haslam A, Wagner Robb S, Hébert JR, Huang H, Wirth MD, Shivappa N, et al. The association between Dietary Inflammatory Index scores and the prevalence of colorectal adenoma. Public health Nutr. 2017;20:1609–16.
18. Sardo Molmenti CL, Steck SE, Thomson CA, Hibler EA, Yang J, Shivappa N, et al. Dietary inflammatory index and risk of colorectal adenoma recurrence: a pooled analysis. Nutr Cancer. 2017;69:238–47.
19. Shivappa N, Godos J, Hébert JR, Wirth MD, Piuri G, Speciani AF, et al. Dietary inflammatory index and colorectal cancer risk-a meta-analysis. Nutrients. 2017;9:1043.
20. Sánchez-Alcoholado L, Ramos-Molina B, Otero A, Laborda-Illanes A, Ordóñez R, Medina JA, et al. The role of the gut microbiome in colorectal cancer development and therapy response. Cancers. 2020;12:1406.
21. Vipperla K, O'Keefe SJ. Diet, microbiota, and dysbiosis: a 'recipe' for colorectal cancer. Food Funct. 2016;7:1731–40.
22. Zhang Y, Yu X, Yu E, Wang N, Cai Q, Shuai Q, et al. Changes in gut microbiota and plasma inflammatory factors across the stages of colorectal tumorigenesis: a case-control study. BMC Microbiol. 2018;18:92.
23. Prorok PC, Andriole GL, Bresalier RS, Buys SS, Chia D, Crawford ED, et al. Design of the prostate, lung, colorectal and ovarian (PLCO) cancer screening trial. Control Clin Trials. 2000;21:273s–309s.
24. Schoen RE, Pinsky PF, Weissfeld JL, Yokochi LA, Church T, Laiyemo AO, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N. Engl J Med. 2012;366:2345–57.
25. Kitahara CM, Berndt SI, de González AB, Coleman HG, Schoen RE, Hayes RB, et al. Prospective investigation of body mass index, colorectal adenoma, and colorectal cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. J Clin Oncol. 2013;31:2450–9.
26. Subar AF, Thompson FE, Kipnis V, Midthune D, Hurwitz P, McNutt S, et al. Comparative validation of the Block, Willett, and National Cancer Institute food frequency questionnaires: the Eating at America's Table Study. Am J Epidemiol. 2001;154:1089–99.
27. Subar AF, Ziegler RG, Thompson FE, Johnson CC, Weissfeld JL, Reding D, et al. Is shorter always better? Relative importance of questionnaire length and cognitive ease on response rates and data quality for two dietary questionnaires. Am J Epidemiol. 2001;153:404–9.
28. Rothman KJ, Greenland S, Lash TL. Introduction to stratified analysis. In: Modern epidemiology, introduction to stratifies analysis. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008. p. 261–3.
29. Tahir MR, Tran QX, Nikulin MS. Comparison of hypertabastic survival model with other unimodal hazard rate functions using a goodness-of-fit test. Stat Med. 2017;36:1936–45.
30. Yuan F, Deng L, Sun X, Chen Z, Shivappa N, Sheth AK, et al. Dietary inflammatory index and risk of colorectal adenoma: effect measure modification by race, nonsteroidal anti-inflammatory drugs, cigarette smoking and body mass index? Cancer Causes Control: CCC. 2021;32:837–47.
31. Obón-Santacana M, Romaguera D, Gracia-Lavedan E, Molinuevo A, Molina-Montes E, Shivappa N, et al. Dietary inflammatory index, dietary non-enzymatic antioxidant capacity, and colorectal and breast cancer risk (MCC-Spain Study). Nutrients. 2019;11:1406.
32. Wirth MD, Shivappa N, Steck SE, Hurley TG, Hébert JR. The dietary inflammatory index is associated with colorectal cancer in the National Institutes of Health-American Association of Retired Persons Diet and Health Study. Br J Nutr. 2015;113:1819–27.
33. Shivappa N, Zucchetto 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;114:152–8.
34. Sharma I, Zhu Y, Woodrow JR, Mulay S, Parfrey PS, McLaughlin JR, et al. Inflammatory diet and risk for colorectal cancer: a population-based case-control study in Newfoundland, Canada. Nutrition. 2017;42:69–74.
35. Harmon BE, Wirth MD, Boushey CJ, Wilkens LR, Draluck E, Shivappa N, et al. The dietary inflammatory index is associated with colorectal cancer risk in the multiethnic cohort. J Nutr. 2017;147:430–8.
36. Cho YA, Lee J, Oh JH, Shin A, Kim J. Dietary inflammatory index and risk of colorectal cancer: a case-control study in Korea. Nutrients. 2016;8:469.
37. Bailey RL, Gahche JJ, Miller PE, Thomas PR, Dwyer JT. Why US adults use dietary supplements. JAMA Intern Med. 2013;173:355–61.
38. Mulholland CA, Benford DJ. What is known about the safety of multivitamin-multimineral supplements for the generally healthy population? Theoretical basis for harm. Am J Clin Nutr. 2007;85:318s–322s.
39. Ronis MJJ, Pedersen KB, Watt J. Adverse effects of nutraceuticals and dietary supplements. Annu Rev Pharm Toxicol. 2018;58:583–601.
40. Ashmore JH, Lesko SM, Miller PE, Cross AJ, Muscat JE, Zhu J, et al. Association of dietary and supplemental iron and colorectal cancer in a population-based study. Eur J Cancer Prev. 2013;22:506–11.
41. Oliai Araghi S, Kiefte-de Jong JC, van Dijk SC, Swart KMA, van Laarhoven HW, van Schoor NM, et al. Folic acid and vitamin B12 supplementation and the risk of cancer: long-term follow-up of the B vitamins for the prevention of osteoporotic fractures (B-PROOF) trial. Cancer Epidemiol, Biomark Prev. 2019;28:275–82.
42. Bairati I, Meyer F, Gélinas M, Fortin A, Nabid A, Brochet F, et al. Randomized trial of antioxidant vitamins to prevent acute adverse effects of radiation therapy in head and neck cancer patients. J Clin Oncol. 2005;23:5805–13.
43. Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N. Engl J Med. 1996;334:1150–5.
44. Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N. Engl J Med. 1994;330:1029–35.
45. Glebov OK, Rodriguez LM, Nakahara K, Jenkins J, Cliatt J, Humbyrd CJ, et al. Distinguishing right from left colon by the pattern of gene expression. Cancer Epidemiol, Biomark Prev. 2003;12:755–62.
46. Zamora-Ros R, Shivappa N, Steck SE, Canzian F, Landi S, Alonso MH, et al. Dietary inflammatory index and inflammatory gene interactions in relation to colorectal cancer risk in the Bellvitge colorectal cancer case-control study. Genes Nutr. 2015;10:447.
47. Tabung FK, Steck SE, Ma Y, Liese AD, Zhang J, Caan B, et al. The association between dietary inflammatory index and risk of colorectal cancer among postmenopausal women: results from the Women's Health Initiative. Cancer Causes Control: CCC. 2015;26:399–408.
48. Gualco G, Reissenweber N, Cliché I, Bacchi CE. Flat elevated lesions of the colon and rectum: a spectrum of neoplastic and nonneoplastic entities. Ann diagnostic Pathol. 2006;10:333–8.
49. Nawa T, Kato J, Kawamoto H, Okada H, Yamamoto H, Kohno H, et al. Differences between right- and left-sided colon cancer in patient characteristics, cancer morphology and histology. J Gastroenterol Hepatol. 2008;23:418–23.
50. Haggar FA, Boushey RP. Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. Clin Colon Rectal Surg. 2009;22:191–7.
51. Festa A, D'Agostino R Jr., Howard G, Mykkänen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation. 2000;102:42–47.
52. Bruce WR, Giacca A, Medline A. Possible mechanisms relating diet and risk of colon cancer. Cancer Epidemiol, Biomark Prev. 2000;9:1271–9.
53. Grosso G, Godos J, Lamuela-Raventos R, Ray S, Micek A, Pajak A, et al. A comprehensive meta-analysis on dietary flavonoid and lignan intake and cancer risk: Level of evidence and limitations. Mol Nutr Food Res. 2017;61:1600930.
54. Gilsing AM, Fransen F, de Kok TM, Goldbohm AR, Schouten LJ, de Bruïne AP, et al. Dietary heme iron and the risk of colorectal cancer with specific mutations in KRAS and APC. Carcinogenesis. 2013;34:2757–66.
55. Zhu Y, Wang PP, Zhao J, Green R, Sun Z, Roebothan B, et al. Dietary N-nitroso compounds and risk of colorectal cancer: a case-control study in Newfoundland and Labrador and Ontario, Canada. Br J Nutr. 2014;111:1109–17.
56. Diggs DL, Huderson AC, Harris KL, Myers JN, Banks LD, Rekhadevi PV, et al. Polycyclic aromatic hydrocarbons and digestive tract cancers: a perspective. J Environ Sci Health Part C, Environ Carcinogenesis Ecotoxicol Rev. 2011;29:324–57.
57. Dvorak HF. Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. N. Engl J Med. 1986;315:1650–9.
58. Gao R, Davis A, McDonald TO, Sei E, Shi X, Wang Y, et al. Punctuated copy number evolution and clonal stasis in triple-negative breast cancer. Nat Genet. 2016;48:1119–30.
59. Cross W, Kovac M, Mustonen V, Temko D, Davis H, Baker AM, et al. The evolutionary landscape of colorectal tumorigenesis. Nat Ecol Evol. 2018;2:1661–72.
60. 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;17:1825–33.

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AUTHOR CONTRIBUTIONS

ZYL and XLJ conceived and designed the analysis. ZYL, HC and HL collected and processed the data. NS and JRH calculated E-DII scores. ZYL and KW performed the analysis. ZYL wrote the paper. ZYL, KW, JRH and XLJ revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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COMPETING INTERESTS

Dr. JRH owns controlling interest in Connecting Health Innovations LLC (CHI), a company that has licensed the right to his invention of the dietary inflammatory index (DII®) from the University of South Carolina in order to develop computer and smartphone applications for patient counselling and dietary intervention in clinical settings. Dr. NS is an employee of CHI. The subject matter of this paper will not have any direct bearing on that work, nor has that activity exerted any influence on this project. The remaining authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Institutional Review Board of the National Cancer Institute approved the study protocol of PLCO Cancer Screening Trial, and all participants provided a written informed consent.

CONSENT TO PUBLISH

Not applicable.

ADDITIONAL INFORMATION

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