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Inflammatory potential of the diet and colorectal tumor risk in persons with Lynch syndrome

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ABSTRACT

Background: Persons with Lynch syndrome (LS) have high lifetime risk of developing colorectal tumors (CRTs) because of a germline mutation in one of their mismatch repair (MMR) genes. An important process in the development of CRTs is inflammation, which has been shown to be modulated by diet.

Objective: We aimed to investigate the association between the inflammatory potential of the diet and the risk of CRTs in persons with LS.

Design: We used the dietary intake of 457 persons with LS from a prospective cohort study to calculate the adapted dietary inflammatory index (ADII). The ADII was split into tertiles in which the highest tertile reflects the most proinflammatory potential of the diet. Cox proportional hazard models, with robust sandwich variance estimates to adjust for dependency within families, were used to calculate HRs and 95% CIs of CRTs by ADII tertile. HRs were adjusted for age, smoking status, and education level, and number of colonoscopies as a time-dependent variable. A potential effect measure modification was explored by stratifying the results by mutated MMR gene, sex, and a history of CRTs. We performed sensitivity analyses by repeating the analyses in non–nonsteroidal anti-inflammatory drug (NSAID) users (n = 315).

Results: During a median follow-up time of 59 mo, 200 participants (43.8%) developed CRTs. No significant association was shown between highest compared with lowest ADII tertiles (HR for highest compared with lowest tertiles: 1.37; 95% CI: 0.80, 2.34). Stratification by mutated MMR gene, sex, and CRT history did not show significantly differential associations (P-interactions $\geq$ 0.64). In non-NSAID users, an HR of 1.60 (95% CI: 0.88, 2.93) for highest compared with lowest tertiles was shown. No significant effect modification was shown in this group either (P-interactions $\geq$ 0.24).

Conclusion: A proinflammatory potential of the diet does not seem to be significantly associated with CRT risk in persons with LS. *Am J Clin Nutr* 2017;106:1287–94.

Keywords: adapted dietary inflammatory index, colorectal adenoma, colorectal carcinoma, colorectal tumor, dietary inflammatory index, hereditary nonpolyposis colorectal cancer, inflammation, Lynch syndrome, mismatch repair

INTRODUCTION

Lynch syndrome (LS) is the most commonly occurring type of hereditary colorectal cancer and is responsible for 1–3% of the total colorectal cancer burden (1). This autosomal dominant condition is caused by germline mutations in DNA mismatch repair (MMR) genes [i.e., MutL homolog 1 (*MLH1*), MutS homolog (*MSH*) 2, *MSH6*, or PMS1 homolog 2 (*PMS2*) (2)] or by a mutation in the epithelial cell adhesion molecule gene, which causes epigenetic silencing of *MSH2* (3). Carriers of these gene mutations have an increased risk of developing colorectal adenomas, and the subsequent progression to carcinomas is accelerated compared with noncarriers (4–6). Depending on the mutated gene, persons with LS have a lifetime risk of 22–79% of developing colorectal cancer before the age of 70 y compared with ~5% in the general population (3, 7–9).

The high variability in lifetime risk of developing colorectal adenomas and carcinomas [i.e., colorectal tumors (CRTs)] in persons with LS, even if they carry the same mutation, supports the need to investigate potential modifiable risk factors. Diet has consistently been shown to modulate inflammation (10). Chronic (low-grade) inflammation has been directly linked to higher risk of developing cancer in general (11, 12). The role of low-grade inflammation in the development of CRTs has been well established by the results of several observational and intervention studies (13, 14). In addition, nonsteroidal anti-inflammatory drugs (NSAIDs) decreased risks of sporadic as well as hereditary CRTs in many observational studies and randomized controlled trials (15–17). However, because the use of aspirin and other NSAIDs is associated with adverse side effects, such as gastrointestinal

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Abbreviations used: ADII, adapted dietary inflammatory index; CRT, colorectal tumor; DII, dietary inflammatory index; FFQ, food-frequency questionnaire; LS, Lynch syndrome; *MLH1*, MutL homolog 1; MMR, mismatch repair; *MSH*, MutS homolog; NSAID, nonsteroidal anti-inflammatory drug.

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bleeding, alternatives to the use of NSAIDs should be explored (18–21).

Dietary patterns are related to levels of inflammatory cytokines (10). Therefore, Cavicchia et al. (22) developed and validated the dietary inflammatory index (DII), which assesses the inflammatory potential of the diet on the basis of literature-derived dietary inflammatory weights of energy and several nutrients (22, 23). Subsequently, van Woudenbergh et al. (24) developed and validated the adapted dietary inflammatory index (ADII). This adjusted DII reduces the between-person variation in dietary intake, avoids the variation in the DII that is driven by a few dietary components with a large range in intake, and avoids an overestimation of the inflammatory effects of energy, fat, and ethanol.

With the use of these indexes, it was observed that a diet with a high inflammatory potential was associated with a 20–22% increased incidence of sporadic colorectal cancer in 2 prospective cohort studies in postmenopausal women (25, 26). Similar associations were reported in 3 case-control studies and 2 prospective cohort studies, which included men and women of all ages (27–31). However, in the prospective studies, increased associations in both men and women were shown, but they were not always significant in women (30, 31).

Hence, diet may be a promising modifiable alternative to the use of NSAIDs to decrease chronic low-grade inflammation and, consequently, the development of CRTs in persons with LS. Therefore, we aimed to prospectively investigate the association between the inflammatory potential of the diet and risk of CRTs in MMR gene-mutation carriers.

METHODS

Study population

In this study, we used data from participants of the GEOLynch (Genetic, Environmental and Other factors that influence tumor risk in persons with LS) study (32). Briefly, this prospective cohort study started in 2006 after approval of the Medical Ethical Review Committee Region Arnhem-Nijmegen. Persons with LS (i.e., with a confirmed mutation in one of the DNA MMR genes *MLH1*, *MSH2*, *MSH*6, or *PMS2*) were included. Between July 2006 and July 2008, eligible participants were identified through the Netherlands Foundation for the Detection of Hereditary Tumors in Leiden, the Radboud University Medical Center in Nijmegen, and the University Medical Center in Groningen, Netherlands. Participants were aged 18–80 y and had to be Dutch speaking and mentally competent to participate and undergo regular colonoscopy surveillance. Exclusion criteria included terminally ill participants, those living outside Netherlands, and those with familial adenomatous polyposis, inflammatory bowel diseases, proctocolectomy, or colostomy, which resulted in 686 presumed eligible participants. Seventy-three percent of subjects (n = 501) agreed to participate and gave written informed consent (**Figure 1**). Nine participants appeared ineligible after signing the informed consent and were excluded. In addition, for this study, participants with incomplete questionnaires (n = 11), incomplete medical data (n = 23), or who were pregnant (n = 1) were excluded, thereby resulting in 457 participants for the analyses.

Exposure assessment

Dietary intake was assessed with the use of a self-administered food-frequency questionnaire (FFQ) that was developed and validated by the Division of Human Nutrition, Wageningen University & Research (33, 34). The FFQ contained 183 items and was designed to assess habitual food intake during the previous month by asking the frequency and amounts of eaten food items. All food items were converted to intakes of energy and nutrients with the use of the Dutch Food Composition Database 2006. Caffeine intake was not included in the Dutch Food Composition Database and, therefore, was estimated on the basis of mean caffeine concentrations of 68.0 mg/100 g coffee (35) and 20 mg/100 g black or green tea (36).

We assessed the inflammatory potential of the diet by calculating the ADII as described by van Woudenbergh et al. (24). Briefly, we used the residual method (37) to retrieve energy-adjusted intakes of SFAs, *trans* fatty acids, carbohydrates, cholesterol, vitamin B-12, iron, protein, MUFAs, riboflavin, thiamine, caffeine, ω-6 PUFAs, ω-3 PUFAs, folate, selenium, niacin, ethanol, zinc, vitamin B-6, vitamin A, vitamin E, vitamin C, vitamin D, quercetin, magnesium, tea, β-carotene, and fiber. Intakes of eugenol, flavan-3-ol, flavones, flavonones, isoflavones, anthocyanidins, garlic, ginger, saffron, pepper, thyme or oregano, rosemary, onions, and turmeric could not be calculated with the FFQ and, therefore, were not taken into account to investigate the inflammatory potential of the diet. Subsequently, energy-adjusted intakes were standardized by subtracting the participants' mean intake from the individual intake and dividing the difference by the SD of the participants' intake, which resulted in an individual z score for each food component. Next, z scores were multiplied by their corresponding inflammatory weights (**Table 1**) (23). An inflammatory weight of zero was allocated to ethanol if ethanol intake was >40 g/d because the anti-inflammatory effects of ethanol seem to diminish with intake >40 g/d (38). The multiplied z scores were subsequently summed to create one ADII score in which a negative score indicated an anti-inflammatory potential of the diet, whereas a positive score indicated a proinflammatory potential of the diet.

Identification of CRT cases

Participants were followed prospectively by regularly reviewing medical records and pathology reports to obtain medical information about performed colonoscopies, surgical interventions, and diagnoses of colorectal adenomas and carcinomas. Also, information on all previously performed colonoscopies, surgical interventions, and diagnoses of colorectal adenomas and carcinomas was collected.

Covariate assessment

Demographic and lifestyle information was collected through a self-administered questionnaire about current height and weight; sex; date of birth; education level [low (i.e., finished primary school or lower vocational or lower general secondary education); middle (i.e., finished general secondary school, preuniversity education, or vocational education); and high (i.e., finished higher professional education or university)]; smoking habits (current, former, or never); NSAID use [never (i.e., <1 time/mo) compared with ever (i.e., ≥1 time/mo)]; and physical activity. BMI

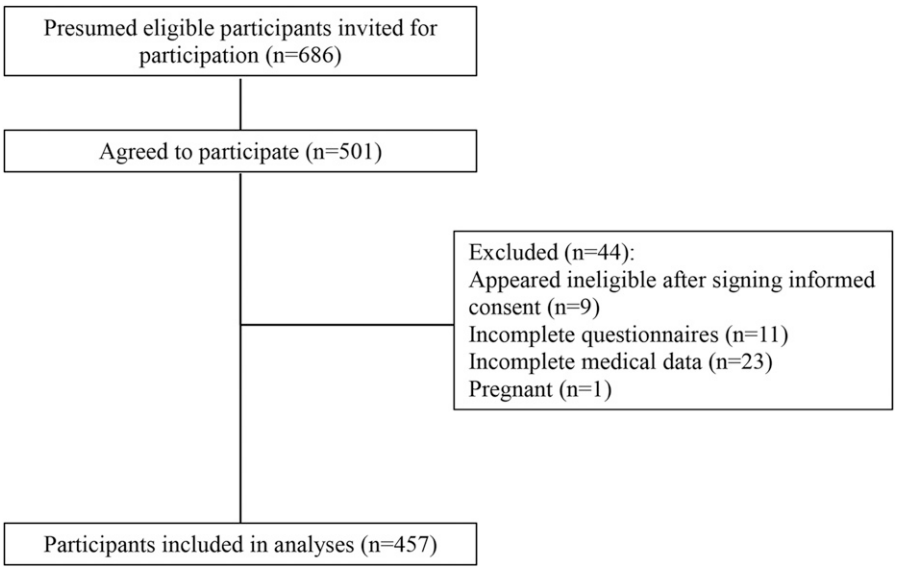

FIGURE 1 Flowchart of included participants between July 2006 and July 2008 in the GEOLynch cohort study.

(in kg/m^2) was calculated by dividing the weight by the square of height and subsequently categorized as overweight (BMI ≥25) or not (BMI <25) (39). Physical activity was measured with a modified Baecke questionnaire (40, 41) and categorized into tertiles representing an inactive, moderately active, or highly active lifestyle.

Data analyses

Summary statistics were used to describe the baseline characteristics of the total cohort and stratified by ADII tertiles with the lowest tertile reflecting the most anti-inflammatory diet. Differences in baseline characteristics between ADII tertiles were tested with the use of a chi-square test or Fisher's exact test for categorical variables and an ANOVA or Kruskall-Wallis test for continuous variables. The contribution of the individual dietary components to the variation in the ADII between participants was assessed with the use of forward linear regression. The partial R^2 of the components in the final model was used to estimate those components' contributions to the ADII, which was adjusted for the influence of other included dietary components.

Cox proportional hazard models were used to calculate HRs and 95% CIs of the association between the inflammatory potential of the diet, as reflected by the ADII score, and risk of developing CRTs. A robust sandwich-covariance estimate was used to account for the dependence of observations within families (42, 43). The person time started on the colonoscopy date that was closest to the questionnaire completion and ended on the date halfway between the colonoscopy in which the first pathology-confirmed CRT was diagnosed and the previous clean colonoscopy. Participants without a CRT diagnosis during follow-up were censored at the date of their last known colonoscopy. Participants who died during follow-up (n = 31) were censored at their last clean colonoscopy if no CRT was diagnosed before death. Nine participants were included in a trial during follow-up and, hence, were censored to prevent an interference with our results. Their person time ended at the date of their last known colonoscopy before trial inclusion if no CRT was diagnosed before that date.

The selection of potential confounders was based on literature and a significant association with the exposure and outcome in univariate analyses. HRs were adjusted for age (years), smoking status, and education level, and number of colonoscopies as a time-dependent covariate. In addition, in the main analysis in all participants, a model was run that also included BMI and physical activity because published studies have shown that BMI and physical activity are associated with CRT risk (32, 44). Tests for linear trend across tertiles were conducted by modeling the median value of each tertile as a continuous variable in the model. The proportionality assumption was tested for significance with Schoenfeld residuals. All covariates met the proportional hazard assumption.

Stratification by the 2 predominant mutated genes (*MLH1* and *MSH2*) by sex and by a history of CRTs was performed to explore the potential effect-measure modification. Interaction terms between the covariate and the ADII tertiles were added to the model to determine a significant ($P < 0.05$) heterogeneity across the strata.

To investigate whether NSAID use affects the association between ADII and CRTs, NSAID users (i.e., those who used NSAIDs ≥1 time/mo) were excluded in the sensitivity analyses, which left 69% of the cohort (n = 315). All statistical tests were 2 sided, and $P < 0.05$ was considered significant. Data were analyzed with the use of SAS software version 9.3 of the SAS System for Windows (SAS Institute Inc.).

RESULTS

During a median follow-up time of 58.8 mo (quartile 1–quartile 3: 33.7–74.8 mo), 200 individuals (43.8%) developed a CRT (182 colorectal adenomas and 18 colorectal carcinomas). ADII scores ranged from −11.7 to 8.4 with a mean ± SD of −0.9 ± 2.6 (**Table 2**). The variance in ADII scores was mainly explained by intake of quercetin (48%) followed by that of folic acid (15%) and *trans* fatty acids (14%) (**Table 3**). Individuals in the first ADII tertile (i.e., with the most anti-inflammatory

TABLE 1
Dietary components included in the adapted dietary inflammatory index and their inflammatory weights

Component	Inflammatory weight[1]
SFAs, g/d	0.373
trans Fatty acid, g/d	0.229
Cholesterol, mg/d	0.110
Vitamin B-12, μg/d	0.106
Carbohydrate, g/d	0.097
Iron, mg/d	0.032
Protein, g/d	0.021
MUFAs, g/d	−0.009
Riboflavin, mg/d	−0.068
Thiamine, mg/d	−0.098
Caffeine, g/d	−0.110
n–6 PUFAs, g/d	−0.159
Folate, μg/d	−0.190
Selenium, mg/d	−0.191
Niacin, mg/d	−0.246
Ethanol,[2] g/d	−0.278
Zinc, mg/d	−0.313
Vitamin B-6, mg/d	−0.365
Vitamin A, μg /d	−0.401
Vitamin E, mg/d	−0.419
Vitamin C, mg/d	−0.424
n–3 PUFAs, g/d	−0.436
Vitamin D, μg/d	−0.446
Quercetin, mg/d	−0.467
Magnesium, mg/d	−0.484
Tea,[3] g/d	−0.536
β-Carotene, μg/d	−0.584
Fiber, g/d	−0.663

[1] Dietary components with a positive inflammatory weight were considered proinflammatory, whereas those with a negative inflammatory weight were considered anti-inflammatory (23).

[2] Ethanol is not likely to be anti-inflammatory when intake is >40 g/d (38). Hence, the dietary inflammatory weight was assumed to be zero for alcohol intake >40 g/d.

[3] Tea intake was included because epicatechin intake could not be calculated.

potential of the diet) were significantly older, less often current smokers, and had higher energy intakes than those of individuals in the second ADII tertile (i.e., hardly any proinflammatory or anti-inflammatory potential of the diet) and third ADII tertile (i.e., with the most proinflammatory potential of the diet) (Table 2).

ADII and CRT risk in all participants

An HR of 1.37 (95% CI: 0.80, 2.34) for CRT risk was shown in participants in the third ADII tertile compared with in participants in the first ADII tertile after correction for the effect of age, smoking status, education level, and number of colonoscopies during follow-up (**Table 4**). No significant linear trend across the ADII tertiles was observed (*P*-trend = 0.33). The risk estimate did not change after further adjusting for BMI and physical activity (HR for ADII tertile 3 compared with tertile 1: 1.44; 95% CI: 0.88, 2.34; *P*-trend = 0.25) (data not shown).

Stratified CRT risk estimates in all participants

Stratification by mutated gene resulted in HRs of 1.67 (95% CI: 0.90, 3.12) and 1.29 (95% CI: 0.52, 3.18) in participants with mutated *MLH1* and *MSH2* genes, respectively, in the third ADII tertile compared with in the first ADII tertile, which were not significantly different (*P*-interaction = 0.64) (**Supplemental Table 1**).

In addition, significantly different HRs were not shown after stratification by sex or CRT history when participants in the third ADII tertile were compared with participants in the first ADII tertile in the adjusted model (*P*-interactions = 0.66 and 0.82, respectively) (Supplemental Table 1).

ADII and CRT risk in non-NSAID users

In the sensitivity analyses, NSAID users were excluded, which left 315 individuals with a median follow-up time of 59.2 mo (quartile 1–quartile 3: 31.2–74.8) in which 145 (46%) individuals were diagnosed with a CRT (133 colorectal adenomas and 12 colorectal carcinomas). Compared with individuals in the first ADII tertile, individuals in the third ADII tertile had an HR of 1.60 (95% CI: 0.88, 2.93) of developing CRTs (Table 4). No linear trend across the ADII tertiles was observed (*P*-trend = 0.15).

Stratified CRT risk estimates in non-NSAID users

Stratification of the non-NSAID users by mutated gene resulted in an increased HR in *MLH1* mutation carriers (**Supplemental Table 2**). For these carriers, an HR of 2.36 (95% CI: 1.05, 5.30) was shown for individuals in the third ADII tertile compared with those in the first ADII tertile. In non-NSAID-using *MSH2* mutation carriers, an HR of 1.17 (95% CI: 0.45, 3.06) was shown (Supplemental Table 2). Again, the associations were not significantly different between *MLH1* and *MSH2* mutation carriers (*P*-interaction = 0.52). Stratifying the results of participants who did not use NSAIDs by sex or history of CRT did not show significant interactions when participants in the third ADII tertile were compared with participants in the first ADII tertile (*P*-interactions = 0.24 and 0.55, respectively) (Supplemental Table 2).

DISCUSSION

We did not observe a significant association between a proinflammatory potential of the diet and risk of LS-associated CRTs. Repeating the analyses in non-NSAID users only revealed a slightly higher, but still not significant, HR.

To the best of our knowledge, this is the first study to investigate the association between the inflammatory potential of the diet and CRT risk in persons with a genetic predisposition to cancer. Earlier studies have been performed on the inflammatory potential of the diet and colorectal cancer risk in the general population. In those studies, increased risks of 20–116% were shown when individuals with the most proinflammatory potential of their diets were compared with individuals with the most anti-inflammatory potential of their diets (25–31). In our study, we showed nonsignificant results in the same direction with an HR of 1.37 (95% CI: 0.80, 2.34) when all participants were included and an HR of 1.60 (95% CI: 0.88, 2.34) in non-NSAID users only. Associations in the same direction in non-NSAID users for colorectal cancer risk were shown in postmenopausal women by Shivappa et al. (25) with an HR for quintile 5 compared with quintile 1 of 2.02 (95% CI: 1.21, 3.39) and, by Tabung et al. (26), with an HR for quintile 5 compared with quintile 1 of

TABLE 2
Baseline characteristics of participants by tertiles of the ADII (n = 457)[1]

	ADII			
	All participants (−11.7 to 8.4)	Tertile 1 (−11.7 to <−1.8)	Tertile 2 (−1.8 to <0.3)	Tertile 3 (0.3–8.4)
n	457	152	152	153
Age,[2] y	49.5 ± 11.5[3]	52.0 ± 10.8	50.1 ± 11.6	46.4 ± 11.6
Follow-up time, mo	58.8 (33.3–73.9)[4]	52.5 (33.3–73.9)	59.3 (35.8–76.0)	59.6 (30.3–75.7)
Men	187 (40.9)	67 (44.1)	60 (39.5)	60 (39.2)
BMI ≥25 kg/m^2, *n* (%)	191 (41.8)	55 (36.2)	61 (40.1)	75 (49.0)
Education level,[5] *n* (%)				
Low	143 (31.3)	45 (29.6)	42 (27.6)	56 (36.6)
Middle	151 (33.0)	42 (27.6)	59 (38.8)	50 (32.7)
High	158 (34.6)	64 (42.1)	49 (32.2)	45 (29.4)
Physical activity tertiles,[5] *n* (%)				
Low	146 (32.0)	44 (28.9)	42 (27.6)	60 (39.2)
Moderate	155 (33.9)	50 (32.9)	57 (37.5)	48 (31.4)
High	148 (32.4)	56 (36.8)	49 (32.2)	43 (28.1)
Smoking status,[2,5] *n* (%)				
Current	81 (17.7)	15 (9.9)	23 (15.1)	43 (28.1)
Former	201 (44.0)	78 (51.3)	74 (48.7)	49 (32.0)
Never	174 (38.1)	59 (38.8)	54 (35.5)	61 (39.9)
Energy intake,[2] kcal/d	2067.6 (1690.5–2557.0)	2337.5 (1836.6–2719.8)	1952.2 (1614.1–2453.5)	2004.1 (1664.7–2508.7)
Colonoscopies,[6] *n* (%)				
≤2	208 (45.5)	65 (42.8)	72 (47.4)	71 (46.4)
3	129 (28.2)	43 (28.3)	39 (25.7)	47 (30.7)
≥4	120 (26.3)	44 (28.9)	41 (27.0)	35 (22.9)
NSAID use (yes), *n* (%)	132 (28.9)	48 (31.6)	36 (23.7)	48 (31.4)
Colorectal tumor history (yes), *n* (%)	228 (49.9)	78 (51.3)	73 (48.0)	77 (50.3)
MMR genes, *n* (%)				
MLH1	176 (38.5)	61 (40.1)	62 (40.8)	53 (34.6)
MSH2	184 (40.3)	59 (38.8)	57 (37.5)	68 (44.4)
MSH6	94 (20.6)	30 (19.7)	32 (21.1)	32 (20.9)
PMS2	3 (0.7)	2 (1.3)	1 (0.7)	—

[1] ADII, adapted dietary inflammatory index; MMR, mismatch repair; NSAID, nonsteroidal anti-inflammatory drug; *MLH1*, MutL homolog 1; *MSH*, MutS homolog; *PMS2*, PMS1 homolog 2.
[2] $P < 0.05$. Differences between ADII tertiles were tested with the use of a chi-square or Fisher's exact test for categorical variables and an ANOVA or Kruskall-Wallis test for continuous variables.
[3] Mean ± SD (all such values).
[4] Median; quartile 1–quartile 3 in parentheses (all such values).
[5] Sum of percentages does not reach 100% because of 8 missing values for physical activity, 1 missing value for smoking, and 5 missing values for education level.
[6] Total number of colonoscopies during follow-up time.

1.31 (95% CI: 1.05, 1.65). These results could be in line with evidence that has suggested a protective role of anti-inflammatory drugs on CRT risk (15–17) because a pro-inflammatory potential of the diet tended to increase CRT risk especially in non-NSAID users.

A proinflammatory potential of the diet may influence colorectal cancer risk systemically by increasing insulin resistance (45–47). The metabolic consequences of insulin resistance (e.g., hyperinsulinemia) promote colorectal cell proliferation and reduce apoptosis (46). Moreover, diet may also influence focal loss of the epithelial cell barrier function, which may lead to an inflammatory response and, ultimately, colorectal cancer (45). However, the importance of these mechanisms in LS-associated CRT development may be relatively small compared with the influence of the MMR gene mutation that causes microsatellite-instability–high colorectal cancers (48–51). The microsatellite-instability pathway to colorectal cancer is often seen in colorectal cancers of persons with LS but is less common in colorectal cancer in the general population (48, 49). However, the presence of tumor-infiltrating lymphocytes and Crohn-like lymphocytes in many LS-related CRT tissues also indicates an important role of inflammation in LS (52–54). Nevertheless, this local inflammatory response is expected to suppress, instead of promote, tumorigenesis because the presence of tumor-infiltrating lymphocytes in colorectal cancers improves survival (55), and diminishing the immune response that is shown in the mucosa of persons with LS seems to trigger the development of colorectal cancer (56). This inflammatory response is suggested to be a consequence of the loss of (functional) MMR proteins (52, 56) and is, therefore, probably not the results of systemic chronic inflammation as assessed via the ADII. Thus, the nonsignificant findings of our study could reflect reality and might support a hypothesis that a less-proinflammatory diet may be more beneficial to decrease sporadic colorectal cancer in the general population than it is for CRTs in persons with LS.

TABLE 3
Explained interindividual variance in the adapted dietary inflammatory index by dietary components included in the calculation of the adapted dietary inflammatory index (n = 457)[1]

Component	Partial R^2
Quercetin	0.48
Folic acid	0.15
trans Fatty acids	0.14
Vitamin E	0.07
Carbohydrate	0.03
Fiber	0.03
Tea	0.02
MUFAs	0.01
Niacin	0.01
Vitamin D	0.01
Other components	0.04

[1] Forward linear regression was used to calculate the partial R^2. Components that explained >1% of the interindividual variation in the final model are shown.

In this study, most (91.0%) of the diagnosed CRTs during follow-up were colorectal adenomas [i.e., the precursor lesion of colorectal cancer (57)]. Not all colorectal adenomas will progress to cancer. Hence, the association between the inflammatory potential of the diet and colorectal adenoma or colorectal cancer risk may differ. However, to the best of our knowledge, no studies have been published that have investigated the association between the inflammatory potential of the diet and colorectal adenoma risk. Nevertheless, some studies have been performed to investigate the influence of single food items or nutrients or food patterns on CRT risk in (suspected) MMR gene mutation carriers. In the same direction as our results, fruit and fiber, which contain mainly food components with an anti-inflammatory diet potential, seemed to be inversely associated with CRT risk in persons with confirmed or suspected LS (58). Moreover, an HR of 2.16 (95% CI: 1.03, 4.49) for colorectal adenomas risk was shown in carriers of an MMR gene mutation in the highest tertile of the Snack pattern, which is mainly loaded on food items that consist of components with a proinflammatory diet potential, than in the lowest tertile (59). In contrast to what would be expected on the basis of their inflammatory weight, no significant associations for alcohol and vitamin B intakes and CRT risk were shown (58, 60–62). No association between meat intake and CRT risk was shown either (58, 63), which cannot be easily compared with our results because meat contains proinflammatory (e.g., saturated fat) as well as anti-inflammatory (e.g., vitamin B-6) food components. Therefore, on the basis of the results of earlier published studies and our result, we cannot conclude if the influence of the inflammatory potential of the diet may be different for colorectal adenoma risk compared with colorectal cancer risk in persons with LS.

Strengths of the current study include the inclusion of confirmed carriers of MMR gene mutations only, the high participation rate, and the prospective design with a relatively long follow-up. In addition, we were able to measure a large number of potential confounders, and a validated FFQ (33, 34) was used to measure each individual's dietary intake.

In contrast with most published studies, we used the ADII, whereas the DII was used in the majority of studies in which the inflammatory potential of the diet was investigated. In our study, the DII was mostly explained (72%) by the intake of fiber, and repeating the analyses with DII tertiles resulted in similar and weaker associations as with the use of ADII tertiles (data not shown). The ADII better reflected the inflammatory potential of the complete diet in this study. In addition, the ADII has been validated in adults against a summary score of low-grade inflammation including C-reactive protein, IL-6, IL-8, TNF-α, serum amyloid A, and soluble intercellular adhesion molecule 1 (24), whereas the DII has been validated against C-reactive protein, IL-6, TNF-α–receptor 2, and homocysteine (64–66). Hence, the ADII is suitable to estimate the inflammatory potential of the diet and was preferred in this study.

For our ADII calculations, we used 28 of 45 food components with an inflammatory weight (23). Three (total fat, total energy intake, and PUFAs) of the 45 components were excluded to avoid overestimation of the inflammatory effect (24), and 14 of the 45

TABLE 4
HRs (95% CIs) for colorectal tumor risk across tertiles of the ADII for all participants (n = 457) and in non-NSAID users only (n = 315)[1]

			HR (95% CI)	
ADII	Cases, n	Total follow-up time, mo	Crude	Adjusted model[2]
All participants				
Tertile 1	67	7983.5	1.00 (reference)	1.00 (reference)
Tertile 2	57	8393.0	0.80 (0.58, 1.11)	0.70 (0.43, 1.15)
Tertile 3	76	8077.6	1.11 (0.79, 1.57)	1.37 (0.80, 2.34)
P-trend[3]	—	—	0.61	0.33
Non-NSAID users[4]				
Tertile 1	49	5593.4	1.00 (reference)	1.00 (reference)
Tertile 2	39	5817.2	0.76 (0.51, 1.14)	1.01 (0.63, 1.62
Tertile 3	57	5344.2	1.21 (0.83, 1.78)	1.60 (0.88, 2.93)
P-trend[3]	—	—	0.45	0.15

[1] ADII, adapted dietary inflammatory index; NSAID, nonsteroidal anti-inflammatory drug.
[2] Adjusted for age, smoking status, and education level, and for number of colonoscopies as a time-dependent variable.
[3] Two-sided P values for test of linear trend were calculated with the use of median values for each tertile of the ADII.
[4] ADII tertile ranges in non-NSAID users were as follows: tertile 1: −9.1 to <−1.6; tertile 2: −1.6 to <0.3, and tertile 3: 0.3–8.4.

components were excluded because dietary intake could not be measured with the FFQ that was used. All of the unmeasured components had an anti-inflammatory diet potential according to their inflammatory weight with the lowest inflammatory weight being that of turmeric (−0.785) and the highest inflammatory weight being that of rosemary (−0.013). This may have resulted in a nondifferential misclassification and hence an underestimation of the results. However, the ADII measured with 28 included food components still reflects the inflammatory potential of the diet because it has been validated against a summary score of low-grade inflammation (24).

Finally, our study is one of the largest studies with confirmed carriers of MMR gene mutations to date. With our number of participants, a power of ≥80% was reached for an effect size of ≥1.63 at a 5% significance level. Although similar effect estimates have been observed in other publications (27, 29), our effect sizes were mostly <1.63, and thus, our study with 457 participants may still have resulted in limited power.

In conclusion, our results do not show a significant association between a proinflammatory potential of the diet and CRT risk in persons with LS. The results might support previous evidence that CRTs in persons with LS arise from a different pathway than do sporadic CRTs. Verification of these results in another and larger prospective cohort study in persons with LS would be desirable before investigating if and how modifying the diet of persons of LS in clinical practice could be useful to decrease CRT risk.

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