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Dietary intake and tissue biomarkers of omega-6 fatty acids and risk of colorectal cancer in adults: a systematic review and dose-response meta-analysis of prospective cohort studies

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Findings on the associations of dietary/tissue levels of omega-6 polyunsaturated fatty acids (n-6 PUFAs) with the risk of colorectal cancer (CRC) are conflicting. We conducted a dose-response meta-analysis to assess the associations of dietary/tissue levels of n-6 PUFAs [total, linoleic acid (LA), and arachidonic acid (AA)] with CRC risk in adults. Twenty prospective cohort studies with a total sample size of 787,490 participants were included. Comparing extreme intake levels of LA revealed the summary relative risks (RR) of 1.15 (95% confidence interval (CI): 1.05–1.27) for CRC, and 1.30 (95% CI: 1.00–1.68) for rectal cancer, indicating a significant positive association for LA. However, neither total n-6 PUFAs nor AA were associated with cancers. A significant positive association was also found between a 1 gr/day increase in dietary LA intake and risk of colon cancer (RR: 1.01, 95% CI: 1.00–1.02). There were no significant associations between tissue levels of total n-6 PUFAs (RR: 0.94, 95% CI: 0.75–1.19), LA (RR: 0.93, 95% CI: 0.61–1.41), and AA (RR: 0.97, 95% CI: 0.70–1.33) and CRC risk. In conclusion, these findings suggest that dietary intake, but not tissue levels, of LA was associated with an increased risk of colorectal, colon, and rectal cancers. (PROSPERO registration: CRD42024516584).

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INTRODUCTION

Colorectal cancer (CRC) is a prevalent gastrointestinal cancer worldwide [1], with its incidence increasing at an alarming rate and predicted to reach 2.5 million new cases by 2035. CRC is the fourth leading cause of cancer-related deaths worldwide, accounting for more than 900,000 deaths annually [1, 2]. This cancer also imposes a significant economic burden on healthcare systems, highlighting the need for effective preventive strategies.

It is well established that lifestyle factors, including both genetic and environmental influences, play an important role in the etiology of CRC [3]. Of different environmental factors, diet has always been of particular interest. Emerging evidence from epidemiological studies indicates that adherence to a Western-style or high-fat diet is associated with an increased risk of CRC [4], while adherence to Mediterranean or DASH diet is associated with a reduced risk [5, 6]. These dietary patterns have been characterized by differing notably in their content of various fatty acids, particularly omega-6 polyunsaturated fatty acids (n-6 PUFA). However, it remains unclear whether the increased risk of CRC is directly attributable to the effects of these fatty acids or other dietary factors also contribute. Vegetable oils like sunflower, safflower, soybean, corn, and canola oils, nuts, and seeds are other dietary sources of these fatty acids, particularly linoleic acid (LA) [7]. Overall, due to the role of n-6 PUFAs in inflammatory responses, they may increase the risk of some cancers [8, 9]. However, the findings of two systematic reviews reveal that increasing dietary intake of LA, the most abundant n-6 PUFA, does not have a significant effect on inflammatory markers [10, 11]. On the other hand, it has been shown that the conversion rate of dietary LA to AA in humans is low [12]. Overall, the role of dietary LA on inflammation is still unclear. In addition, findings from observational studies on the link between n-6 PUFAs and CRC risk are inconsistent [13–32], with some studies indicated a significant positive association between dietary and tissue biomarkers of n-6 PUFA and risk of CRC [17, 20, 22, 23, 29], while other studies did not report any significant association [13, 15, 20, 22, 24, 27, 28, 31] and even an inverse association [14].

A recent meta-analysis (Lu et al. 2023) summarized available findings on the association between dietary/tissue biomarkers of n-6 PUFA and CRC [33], revealing that the n-6/n-3 PUFA ratio is related to a higher risk of CRC. However, several eligible studies were not included in that meta-analysis [23, 32], and it did not assess the dose-response relationship between dietary n-6 PUFA and CRC risk, focusing only on comparisons between the highest and lowest intake levels. A dose-response analysis provides additional insights into the association between dietary n-6 PUFA and CRC risk, recognizing that fat intake does vary substantially across different populations. Accordingly, we have now conducted

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a comprehensive systematic review and dose-response meta-analysis of all existing prospective cohort studies to provide an improved understanding of association(s) between dietary/tissue biomarkers of n-6 PUFAs and risk of CRC in adults.

METHODS

This systematic review and meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol [34].

Search strategy

We conducted a systematic search using online databases, including PubMed, Scopus, and ISI Web of Science until March 5, 2024, to identify prospective cohort studies that examined the associations between dietary intake and tissue biomarkers of n-6 PUFAs (total, LA, and AA) and risk of CRC. Supplementary Table 1 presented the medical subject heading terms (MeSH) and non-MeSH terms used in the search strategy. In addition to the mentioned databases, we conducted a web-based search in Google Scholar using a combination of "omega-6 fatty acid" and "colorectal cancer" terms. In this search engine, we screened the first 500 papers ranked based on relevancy. In the systematic search, no restrictions were considered for publication time or the language of articles. We also searched the reference lists of the included articles and recent reviews to ensure comprehensive inclusion.

Inclusion criteria

We included prospective studies (e.g., prospective cohort, nested case-control, case-cohort studies), those that recruited adults (≥ 18 years), and reported relative risk (RR) estimates, including hazard ratio (HR), risk ratio (RR), and odds ratio (OR), with 95% confidence interval (CI) for the associations of dietary/tissue biomarkers of n-6 PUFAs (total, LA, AA) with colorectal, colon, or rectal cancers risk or presenting required data for the calculation of these effect sizes. If findings from one dataset were published in more than one article, we selected the one with the greatest number of cases or longer follow-up duration.

Exclusion criteria

We excluded letters, comments, reviews, meta-analyses, animal studies, abstracts, citations, and those studies with insufficient data. We also did not include studies that were conducted on children and adolescents, recruited critically ill participants, had a retrospective design, and considered genetically predicted dietary of n-6 PUFAs. In addition, studies that assessed dietary intake of fatty acids, without considering n-6 PUFAs (total, LA, and AA), were excluded.

Data extraction

Study selection and data extraction were conducted by two independent investigators (NA and NE) and any disagreement between them was resolved by discussion with a third researcher (OS). For the meta-analysis, we extracted any reported relative risk estimates, including RR, HR, and OR, along with 95% CI for the associations of dietary intake and tissue biomarkers of n-6 PUFA (total, LA, and AA) with colorectal, colon, and rectal cancer risk. In the case of studies that reported several risk estimates, we selected the one with the most adjustments. In addition to the risk estimates, we extracted additional information on the first author's name, publication year, cohort name, sample size, number of cases, gender and age of participants, study location, follow-up duration (years), methods used to assess dietary or tissue levels of n-6 PUFA and colorectal cancer diagnosis, and confounding variables adjusted in the statistical analysis. For studies that reported their findings by gender, we considered that study as two separate studies. For the studies that reported main analyses for total population as well as stratified analyses for gender or any other variables, we used the effect size for total population in our primary analysis.

Quality assessment

The quality of studies included in the current meta-analysis was evaluated using the Newcastle Ottawa Scale (NOS) [35]. According to this scale, a maximum of 9 points would be given to each study according to the following parameters: 4 points for selection of participants, 2 points for comparability, and 3 points for the assessment of outcomes. Since the median score of included studies in the current meta-analysis was 7, we considered studies with a score of ≥7 as high-quality studies.

Statistical analysis

We included the relative risks (RRs, HRs, and ORs) of colorectal, colon, and rectal cancers, reported for the comparison between the highest and lowest intakes/tissue levels of n-6 PUFA (total, LA, and AA), into the meta-analysis. Since the relative risks are non-normally distributed variables, we included the natural log form (and its standard error) of these risk estimates into the statistical analyses. To calculate the summary relative risk, a random-effects model was used to take between-study heterogeneity into account. To assess heterogeneity among the included studies, both Q-statistic and I^2 values were used. For the I^2 statistic, values of >50% were considered as significant heterogeneity between studies. In addition to the main analysis, subgroup analyses were conducted based on gender, study location, and study quality. To assess publication bias, we used Egger's regression asymmetry test [36]. For the significant publication bias, the trim-and-fill method was used to detect the effect of probable missing studies on the overall relative risk [37]. Furthermore, sensitivity analysis was conducted to evaluate the dependency of overall effect size on one study. In this analysis, each study was excluded to assess the influence of that study on the overall estimate.

For the linear dose-response analysis, we used the generalized least squares trend (glst command in STATA) estimation method [38, 39]. Firstly, study specific slopes were estimated, and then, these slopes were combined to obtain an overall average slope. Using a random-effects model, the study specific slopes were combined. In the glst method, outcome distribution, the total number of participants, and the effect sizes with the variance estimates for ≥3 quantitative categories of exposure were required. For each study, we assigned the median or mean amount of n-6 PUFA (total, LA, and AA) in each category to the corresponding effect size. For studies that reported the intake of n-6 PUFAs (total, LA, and AA) as the percent of energy (%E), we converted them to gr/day. For studies that reported n-6 PUFA as ranges, the midpoint in each category was estimated. When the highest and lowest categories were open ended, we assumed the length of the open-ended interval to be the same as that of the adjacent interval. Also, a possible non-linear dose-response association was examined using restricted cubic splines with 3 knots at centiles of 10%, 50%, and 90% of the distribution. The correlation within each set of provided risk estimates was accounted for and the study specific estimates were combined by using a linear mixed effects meta-analysis. This method estimates the study specific slopes and combines them to obtain an overall average slope in a single stage. The significance for non-linearity was calculated by null hypothesis testing, in which we considered the coefficient of the second spline to be equal to zero. Statistical analyses were performed using STATA version 14.0. For all tests, including Cochran's Q test, $P < 0.05$ was considered statistically significant.

RESULT

Literature search

4005 articles were retrieved from the initial search (Fig. 1). Following the exclusion of duplicate papers ($n = 1238$) and those that did not meet the inclusion criteria ($n = 2737$), 30 potentially relevant full-text articles were identified. Of the 30 papers, a further 7 articles were excluded. These studies used a case-control design ($n = 4$) [40–43], reporting an overall risk estimate of gastrointestinal cancer, but not CRC ($n = 1$) [44], and reporting colorectal adenoma as an outcome ($n = 2$) [45, 46]. Five duplicate articles were identified, of which two were related to the Netherlands cohort study [31, 47], three to the Nurses' Health Study and Health Professionals Follow-up Study [30, 48, 49]. As these articles evaluated similar exposure variables, we included only the one with higher quality, with the greatest number of cases, or higher follow-up period [30, 31], and excluded others [47–49]. Two other duplicate articles were also identified, and all were included, given that different outcome variables (CRC, colon cancer, and rectal cancer) were investigated [13, 19]. Accordingly, 20 prospective cohort studies were included in the current systematic review and meta-analysis [13–32], of which fourteen evaluated the association between n-6 PUFA and CRC (10 on dietary n-6 PUFA intake [13, 15, 18, 21, 22, 29, 30], 3 on tissue levels of n-6 PUFA [16, 20, 23], and one on both [17]), eleven assessed the link between LA and CRC (7 on dietary LA intake [22, 24, 26, 27, 29, 30, 32], 3 on tissue levels of LA [14, 20, 23], and one on both [17]), nine assessed the relation between AA and CRC (5 on dietary AA intake [22, 24, 26, 29, 30], 3 on tissue levels of AA [14, 20, 23], and one on both [17]). In addition, three studies investigated the relationship between dietary or tissue levels of n-6 PUFA and colon or rectal cancers without considering CRC in relation to dietary or tissue levels of n-6 PUFA [19, 28, 31].

Characteristics of included studies

The characteristics of included studies, published between 1999 and 2021, are summarized in Supplementary Table 2. The number of participants ranged from 460 to 134,017, totaling 787,490, with an age range between 27 and 84 years. Duration of the follow-up ranged from 6 to 26 years, with a total of 10,694 CRC, 5417 colon cancer, and 2533 rectal cancer cases were recorded. Three studies recruited men only [16, 26, 27], five were conducted solely on women [22, 24, 25, 29, 32], and the remaining studies enrolled both genders [23, 28, 30, 31], of which, only four reported sex-stratified effect sizes [15, 20, 28, 30]. Five studies were from the United States (US) [15, 16, 22, 25, 30], one from Australia [17], and seven from European populations [18, 21, 23, 27, 29, 31, 32], and Asian [13, 14, 19, 20, 24, 26, 28] countries. In addition to the assessment of dietary intake at the study baseline, 5 studies repeated this assessment during the follow-up period [15, 24, 26, 28, 30].

Of sixteen studies on dietary intake of n-6 PUFAs, fifteen used food frequency questionnaire [13, 15, 17, 19, 21, 22, 24–32] and one used food diaries [18] for dietary assessment. Two studies collected dietary data through a face-to-face interview [19, 26], and others used self-reported data in their analysis [13, 15, 17, 21, 22, 24, 25, 27–32]. In all studies on tissue levels of n-6 PUFAs, fatty acids were measured in blood [14, 16, 17, 20, 23], and all used chromatography methods to measure n-6 fatty acids concentrations. CRC and its subtypes were determined using data from medical records or cancer registries in thirteen studies [13, 14, 24, 31, 32], self-reported data in five [15, 16, 22, 25, 30], and both medical records and self-reported data in two studies [23, 26]. In the majority of studies, relative risk estimates were adjusted for some important confounders including family history of CRC ($n = 7$), age ($n = 17$), body mass index ($n = 17$), smoking ($n = 17$), alcohol consumption ($n = 17$), physical activity ($n = 14$), energy intake ($n = 16$), and other dietary variables, including processed meat, fiber and calcium ($n = 8$). The NOS scores of the studies ranged from 6 to 9, with a median of 7 Sixteen studies had a score of ≥7, and were, accordingly, considered high-quality studies [13, 14, 32] (Supplementary Tables 3 and 4).

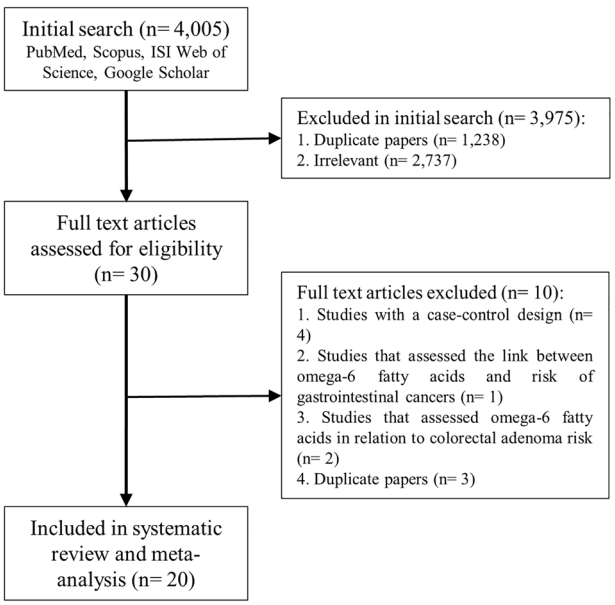

Fig. 1 Flow diagram of study selection.

Findings from the systematic review

None of the included studies revealed a significant association between dietary intake or tissue levels of n-6 PUFAs and the risk of CRC and colon cancer. Of eight studies, investigating the association between dietary intake of n-6 PUFAs and risk of rectal cancer, two reported a positive association [17, 29]. Of studies assessing dietary intake of LA, one study showed a positive association with CRC [29] and two indicated a positive association with rectal cancer [17, 29]. No significant association was found for colon cancer. In contrast, one study revealed a significant inverse association between dietary intake of LA and risk of CRC and colon cancer [14]. No other significant association was seen for tissue levels of LA and AA with risk of CRC, colon, and rectal cancer.

Meta-analysis on n-6 PUFAs and risk of CRC

Dietary n-6 PUFA. Sixteen studies evaluated the association between dietary intake of n-6 PUFAs and risk of CRC [13, 15, 21, 22, 28–30]. Among 738,604 participants included in these studies, 9152 cases of CRC, 3797 cases of colon cancer, and 1676 cases of rectal cancer were recorded during the follow-up period. Comparing the highest categories of dietary n-6 PUFAs intake with the lowest, RR for CRC, was 1.05 (95% CI: 0.94–1.17, $P = 0.38$, $I^2 = 48.9\%$; $P = 0.02$ for heterogeneity), indicating no significant association between dietary n-6 PUFAs intake and CRC risk (Table 1 and Supplementary Fig. 1). Such non-significant association was seen for colon (RR: 1.02, 95% CI: 0.91–1.15, $P = 0.71$, $I^2 = 0.0\%$; $P = 0.88$ for heterogeneity) and rectal (RR: 1.19, 95% CI: 0.93–1.52, $P = 0.18$, $I^2 = 47.6\%$; $P = 0.06$ for heterogeneity) cancers. Fifteen studies were eligible for the linear dose-response analysis of dietary n-6 PUFAs intake and risk of CRC [13, 15, 21, 22, 24, 25, 28–30]. There was no significant linear association between a 1 gr/day increase in dietary n-6 PUFAs intake and the risk of colorectal (RR: 1.00, 95% CI: 0.99–1.01, $P = 0.97$, $I^2 = 41.4\%$; $P = 0.07$ for heterogeneity), colon (RR: 1.00, 95% CI: 0.99–1.01, $P = 0.88$, $I^2 = 0\%$; $P = 1.00$ for heterogeneity), and rectal (RR: 1.01, 95% CI: 0.98–1.03, $P = 0.51$, $I^2 = 61.3\%$; $P = 0.02$ for heterogeneity) cancers (Table 1 and Supplementary Fig. 2). Eleven studies were included in the non-linear dose-

Table 1. Summary risk estimates for association between dietary intake (or tissue levels) of omega-6 fatty acids and the risk of colorectal, colon, and rectal cancer in adults[a].

	No of effect sizes	Pooled relative risk (95% CI)[b]	*P*	I^2 (%)[c]	P-heterogeneity[d]
Dietary intake of n-6 PUFA					
The highest versus lowest comparison					
Colorectal cancer					
Overall	13	1.05 (0.94–1.17)	0.38	48.9	0.02
Subgroup analysis					
Sex					
Men	3	1.06 (0.85–1.31)	0.62	61.7	0.07
Women	6	1.07 (0.88–1.31)	0.48	58.2	0.04
Men and women	4	1.03 (0.84–1.26)	0.78	46.0	0.14
Study location					
US	6	1.01 (0.85–1.20)	0.93	59.9	0.03
Non-US countries	7	1.10 (0.95–1.27)	0.21	38.5	0.14
Study quality[e]					
High quality	11	1.07 (0.95–1.20)	0.30	49.5	0.03
Low quality	2	0.97 (0.68–1.40)	0.88	69.4	0.07
Colon cancer					
Overall	8	1.02 (0.91–1.15)	0.71	0	0.88
Subgroup analysis					
Sex					
Men	3	1.06 (0.89–1.26)	0.50	0	0.47
Women	3	0.95 (0.78–1.16)	0.62	0	0.72
Men and women	2	1.10 (0.79–1.52)	0.58	0	0.84
Study location					
US	2	1.02 (0.85–1.23)	0.84	0	0.35
Non-US countries	6	1.03 (0.88–1.20)	0.75	0	0.83
Rectal cancer					
Overall	8	1.19 (0.93–1.52)	0.18	47.6	0.06
Subgroup analysis					
Sex					
Men	3	1.20 (0.94–1.53)	0.14	0	0.42
Women	3	1.06 (0.55–2.05)	0.86	75.8	0.02
Men and women	2	1.41 (0.82–2.42)	0.22	44.7	0.18
Study location					
US	2	0.98 (0.55–1.75)	0.96	65.2	0.09
Non-US countries	6	1.27 (0.96–1.68)	0.10	44.2	0.11
Linear dose-response association (per 1 g/day increase)					
Colorectal cancer					
Overall	11	1.00 (0.99–1.01)	0.97	41.4	0.07
Subgroup analysis					
Sex					
Men	2	1.00 (0.98–1.02)	1.00	70.7	0.07
Women	6	1.01 (0.99–1.02)	0.45	59.4	0.03
Men and women	3	1.00 (0.99–1.01)	0.42	0	0.59
Study location					
US	6	1.00 (0.99–1.01)	0.86	53.7	0.06
Non-US countries	5	1.00 (0.99–1.01)	0.87	36.1	0.18
Study quality[e]					
High quality	9	1.00 (0.99–1.01)	0.91	45.1	0.07
Low quality	2	1.00 (0.98–1.02)	0.91	59.7	0.12

Table 1. continued

	No of effect sizes	Pooled relative risk (95% CI)[b]	*P*	I^2 (%)[c]	P-heterogeneity[d]
Colon cancer					
Overall	7	1.00 (0.99–1.01)	0.88	0	1.00
Subgroup analysis					
Sex					
Men	2	1.00 (0.99–1.01)	1.00	0	1.00
Women	3	1.00 (0.99–1.01)	0.99	0	0.97
Men and women	2	1.01 (0.98–1.03)	0.58	0	0.72
Study location					
US	2	1.00 (0.99–1.01)	1.00	0	1.00
Non-US countries	5	1.00 (0.99–1.02)	0.72	0	0.99
Rectal cancer					
Overall	7	1.01 (0.98–1.03)	0.51	61.3	0.02
Subgroup analysis					
Sex					
Men	2	1.00 (0.98–1.03)	0.67	0	0.41
Women	3	1.03 (0.95–1.12)	0.43	80.1	0.01
Men and women	2	1.02 (0.97–1.07)	0.49	66.0	0.09
Study location					
US	2	1.00 (0.98–1.02)	0.84	0.70	0.32
Non-US countries	5	1.02 (0.98–1.06)	0.42	71.4	0.01
Tissue levels of n-6 PUFA					
The highest versus lowest comparison					
Colorectal cancer					
Overall	5	0.94 (0.75–1.19)	0.62	0	0.58
Subgroup analysis					
Sex					
Men	2	0.65 (0.40–1.07)	0.09	0	0.86
Women	1	1.15 (0.48–2.75)	0.75	0	<0.001
Men and women	2	1.03 (0.79–1.35)	0.82	0	0.81
Study location					
US	1	0.63 (0.34–1.17)	0.14	0	<0.001
Non-US countries	4	1.01 (0.79–1.29)	0.96	0	0.81
Study quality[e]					
High quality	2	1.03 (0.79–1.35)	0.82	0	0.81
Low quality	3	0.75 (0.49–1.15)	0.19	0	0.53

[a]Abbreviation: *n-6 PUFA* omega-6 polyunsaturated fatty acids, *CI* confidence interval, *US* United States.
[b]Obtained from the random effects model.
[c]Inconsistency- the percentage of variation across studies due to heterogeneity.
[d]Obtained from the *Q*-test.
[e]Studies with a median score of 7 or more, based on the NOS, were considered as a high-quality study.

response analysis [13, 15, 18, 19, 21, 22, 24, 25, 28–30], revealing no evidence of a non-linear association for colorectal ($P = 0.39$ for non-linearity), colon ($P = 0.70$ for non-linearity), and rectal ($P = 0.64$ for non-linearity) cancers in relation to dietary n-6 PUFAs intake (Fig. 2).

Tissue n-6 PUFAs. Four studies assessed the relationship between tissue levels of n-6 PUFAs and CRC risk [16, 17, 20, 23], with a total of 7453 participants and 1811 cases of CRC. There was no significant association between tissue levels of n-6 PUFAs and risk of CRC (RR: 0.94, 95% CI: 0.75–1.19, $P = 0.62$, $I^2 = 0\%$, $P = 0.58$ for heterogeneity) (Table 1 and Supplementary Fig. 3). The number of studies for n-6 PUFAs levels and colon/rectal cancer was not sufficient for a meta-analysis. Also, due to the limited number of studies, performing the dose-response analysis was not possible for all outcomes.

Meta-analysis on LA and risk of CRC

Dietary LA. Ten studies in 9 articles, with a total sample size of 438,873 participants, 5304 cases of CRC, 3485 cases of colon cancer, and 1468 cases of rectal cancer, were included [17, 22, 24, 26, 27, 29–32], for dietary LA analysis. RR for the risk of CRC, comparing the highest categories of dietary LA intake with the lowest categories, was 1.15 (95% CI: 1.05–1.27, $P = 0.003$, $I^2 = 0\%$, $P = 0.44$ for heterogeneity), indicating a significant positive association (Table 2 and Supplementary Fig. 4). Such positive association was seen for colon (RR: 1.10, 95% CI: 0.99–1.23, $P = 0.09$, $I^2 = 0\%$, $P = 0.78$ for heterogeneity) and rectal (RR: 1.30,

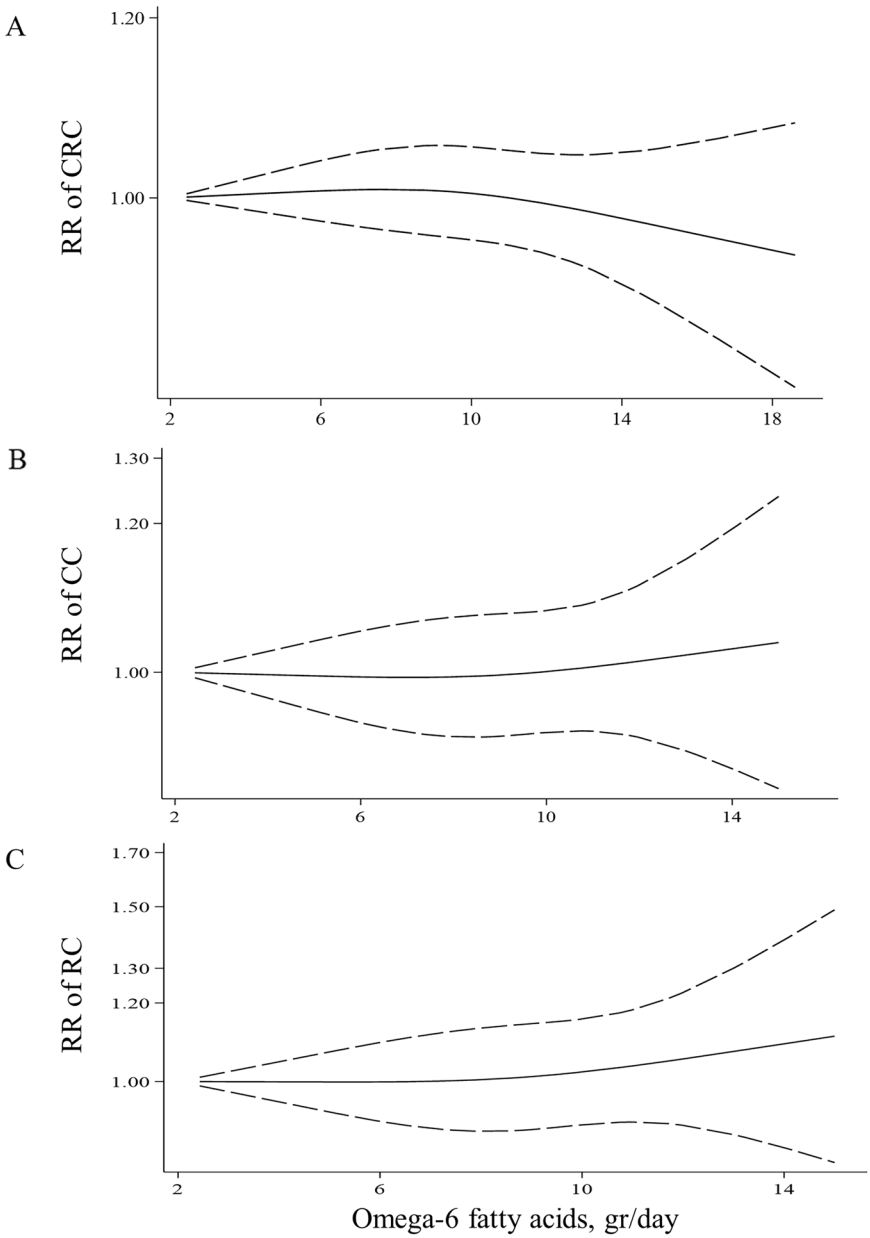

Fig. 2 Non-linear dose-response association between dietary omega-6 fatty acids and colorectal cancer in adults. A Colorectal cancer, **B** colon cancer, and **C** rectal cancer. The solid lines indicate the spline model. The dashed lines present the 95% CI. CRC colorectal cancer, CC colon cancer, RC rectal cancer, RR relative risk.

95% CI: 1.00–1.68, $P = 0.05$, $I^2 = 57.0\%$, $P = 0.03$ for heterogeneity) cancers. However, these associations were marginally significant. Nine studies in 8 articles were eligible for the linear dose-response analysis [17, 22, 24, 27, 29–32], and there was no significant linear association between a 1 gr/day increase in dietary LA intake and risk of CRC (RR: 1.01, 95% CI: 0.99–1.03, $P = 0.12$, $I^2 = 42.1\%$; $P = 0.11$ for heterogeneity) and rectal cancer (RR: 1.03, 95% CI: 1.00–1.06, $P = 0.09$, $I^2 = 76.0$; $P = 0.001$ for heterogeneity). In contrast, a 1 gr/day increase in dietary LA intake was associated with a 1% increased risk of colon cancer (RR: 1.01, 95% CI: 1.00–1.02, $P = 0.02$, $I^2 = 0\%$; $P = 0.60$ for heterogeneity) (Table 2 and Supplementary Fig. 5). Eight studies in 7 articles were included in the non-linear dose-response analysis [22, 24, 27, 29–32], revealing no evidence of non-linearity for the associations between dietary LA intake and risk of colorectal ($P = 0.88$ for non-linearity), colon ($P = 0.44$ for non-linearity) and rectal ($P = 0.41$ for non-linearity) cancers (Fig. 3).

Tissue LA. Five studies in 4 papers assessed the relationship between tissue levels of LA and CRC risk [14, 17, 20, 23], with a total of 7693 participants and recorded 1983 cases of CRC, 211 cases of colon cancer, and 139 cases of rectal cancer. Combining the results from these articles, we found no significant association between tissue levels of LA and CRC risk (RR: 0.93, 95% CI: 0.61–1.41, $P = 0.74$, $I^2 = 69.0\%$, $P = 0.01$ for heterogeneity) (Table 2 and Supplementary Fig. 6). Due to the limited number of studies, we were not able to perform a meta-analysis for colon/rectal cancer and also the dose-response analysis.

Meta-analysis on AA and risk of CRC

Dietary AA. Seven studies, with a total sample size of 346,743 participants and 4659 CRC cases, 2746 colon cancer cases, and 1149 rectal cancer cases, evaluated the association between dietary AA intake and CRC risk [17, 22, 24, 26, 29, 30]. Comparing the highest and lowest categories of dietary AA intake, RR for CRC

Table 2. Summary risk estimates for association between dietary intake (or tissue levels) of linoleic acid and the risk of colorectal, colon, and rectal cancer in adults[a].

	No of effect sizes	Pooled relative risk (95% CI)[b]	*P*	I^2 (%)[c]	P-heterogeneity[d]
Dietary intake of LA					
The highest versus lowest comparison					
Colorectal cancer					
Overall	9	1.15 (1.05–1.27)	0.003	0	0.44
Subgroup analysis					
Sex					
Men	3	1.20 (1.03–1.38)	0.02	0	0.93
Women	5	1.11 (0.94–1.32)	0.22	26.9	0.24
Men and women	1	1.41 (0.99–2.00)	0.05	0	<0.001
Study location					
US	3	1.10 (0.90–1.34)	0.36	43.1	0.17
Non-US countries	6	1.23 (1.08–1.40)	0.002	0	0.77
Colon cancer					
Overall	7	1.10 (0.99–1.23)	0.09	0	0.78
Subgroup analysis					
Sex					
Men	2	1.15 (0.95–1.38)	0.16	0	0.82
Women	3	1.01 (0.84–1.20)	0.95	0	0.73
Men and women	2	1.23 (0.97–1.56)	0.08	0	0.52
Study location					
US	2	1.09 (0.92–1.29)	0.34	0	0.47
Non-US countries	5	1.12 (0.96–1.30)	0.15	0	0.62
Study quality[e]					
High quality	6	1.07 (0.95–1.21)	0.26	0	0.88
Low quality	1	1.31 (0.97–1.77)	0.08	0	<0.001
Rectal cancer					
Overall	7	1.30 (1.00–1.68)	0.05	57.0	0.03
Subgroup analysis					
Sex					
Men	2	1.29 (0.98–1.70)	0.07	0	0.72
Women	3	1.30 (0.66–2.55)	0.45	81.1	0.01
Men and women	2	1.36 (0.79–2.34)	0.27	66.2	0.09
Study location					
US	2	0.92 (0.55–1.56)	0.77	63.6	0.10
Non-US countries	5	1.48 (1.17–1.86)	0.001	24.2	0.26
Study quality[e]					
High quality	6	1.35 (1.00–1.82)	0.05	61.2	0.02
Low quality	1	1.03 (0.66–1.61)	0.90	0	<0.001
Linear dose-response association (per 1 g/day increase)					
Colorectal cancer					
Overall	7	1.01 (0.99–1.03)	0.12	42.1	0.11
Subgroup analysis					
Sex					
Men	2	1.01 (0.99–1.03)	0.44	44.9	0.18
Women	5	1.02 (0.99–1.05)	0.16	52.8	0.08
Study location					
US	3	1.01 (0.99–1.02)	0.51	46.1	0.16
Non-US countries	4	1.02 (0.99–1.05)	0.12	30.6	0.23
Colon cancer					
Overall	6	1.01 (1.00–1.02)	0.02	0	0.60

Table 2. continued

	No of effect sizes	Pooled relative risk (95% CI)[b]	*P*	I^2 (%)[c]	P-heterogeneity[d]
Subgroup analysis					
Sex					
Men	1	1.01 (0.99–1.02)	0.19	0	<0.001
Women	3	1.00 (0.97–1.03)	0.86	35.8	0.21
Men and women	2	1.01 (1.00–1.02)	0.04	0	1.00
Study location					
US	2	1.01 (1.00–1.02)	0.10	0	1.00
Non-US countries	4	1.01 (0.99–1.02)	0.41	16.2	0.31
Study quality[e]					
High quality	5	1.01 (1.00–1.02)	0.18	0	0.48
Low quality	1	1.01 (1.00–1.02)	0.05	0	<0.001
Rectal cancer					
Overall	6	1.03 (1.00–1.06)	0.09	76.0	0.001
Subgroup analysis					
Sex					
Men	1	1.01 (0.98–1.04)	0.51	0	<0.001
Women	3	1.09 (0.97–1.22)	0.15	86.5	0.001
Men and women	2	1.02 (0.98–1.07)	0.36	83.3	0.01
Study location					
US	2	1.00 (0.98–1.02)	0.99	0	0.36
Non-US countries	4	1.06 (1.00–1.12)	0.04	83.4	<0.001
Study quality[e]					
High quality	5	1.04 (1.00–1.09)	0.07	78.3	0.001
Low quality	1	1.00 (0.98–1.02)	1.00	0	<0.001
Tissue levels of LA					
The highest versus lowest comparison					
Colorectal cancer					
Overall	5	0.93 (0.61–1.41)	0.74	69.0	0.01
Subgroup analysis					
Sex					
Men	1	0.57 (0.24–1.37)	0.21	0	<0.001
Women	1	1.88 (0.78–4.53)	0.16	0	<0.001
Men and women	3	0.90 (0.55–1.46)	0.67	78.4	0.01
Study quality[e]					
High quality	3	0.90 (0.55–1.46)	0.67	78.4	0.01
Low quality	2	1.03 (0.32–3.33)	0.96	71.9	0.06

[a]Abbreviation: *LA* linoleic acid, *CI* confidence interval, *US* United States.
[b]Obtained from the random effects model.
[c]Inconsistency- the percentage of variation across studies due to heterogeneity.
[d]Obtained from the *Q*-test.
[e]Studies with a median score of 7 or more, based on the NOS, were considered as a high-quality study.

was 0.97 (95% CI: 0.86–1.10, $P = 0.66$, $I^2 = 25.7\%$; $P = 0.23$ for heterogeneity), indicating a non-significant association between dietary AA intake and CRC risk (Table 3 and Supplementary Fig. 7). Such non-significant association was also observed for colon (RR: 0.97, 95% CI: 0.84–1.10, $P = 0.61$, $I^2 = 0.90\%$; $P = 0.40$ for heterogeneity) and rectal (RR: 0.89, 95% CI: 0.74–1.08, $P = 0.24$, $I^2 = 0\%$; $P = 0.74$ for heterogeneity) cancers. Six studies were eligible for the linear dose-response analysis [17, 22, 24, 29, 30], and there was no linear association between a 100 mg/day increase in dietary AA intake and the risk of colorectal (RR: 1.02, 95% CI: 0.94–1.11, $P = 0.59$, $I^2 = 53.3\%$; $P = 0.07$ for heterogeneity), colon (RR: 1.01, 95% CI: 0.94–1.09, $P = 0.76$, $I^2 = 23.5\%$; $P = 0.27$ for heterogeneity), and rectal (RR: 0.98, 95% CI: 0.93–1.04, $P = 0.52$, $I^2 = 0\%$; $P = 0.80$ for heterogeneity) cancers (Table 3 and Supplementary Fig. 8). The non-linear dose-response also showed no evidence of non-linearity for colorectal ($P = 0.09$ for non-linearity), colon cancer ($P = 0.19$ for non-linearity), and rectal ($P = 0.76$ for non-linearity) cancers in relation to dietary AA intake [22, 24, 29, 30] (Fig. 4).

Tissue AA. Five studies assessed the relationship between tissue levels of AA and CRC risk [14, 17, 20, 23], with a total of 7693 participants, of which 1983 cases of CRC, 881 cases of colon cancer, and cases of 538 rectal cancer were recorded. Combining the results from these studies revealed no significant association between tissue levels of AA and risks of colorectal (RR: 0.97, 95% CI: 0.70–1.33, $P = 0.83$, $I^2 = 45.8\%$, $P = 0.12$ for heterogeneity) and

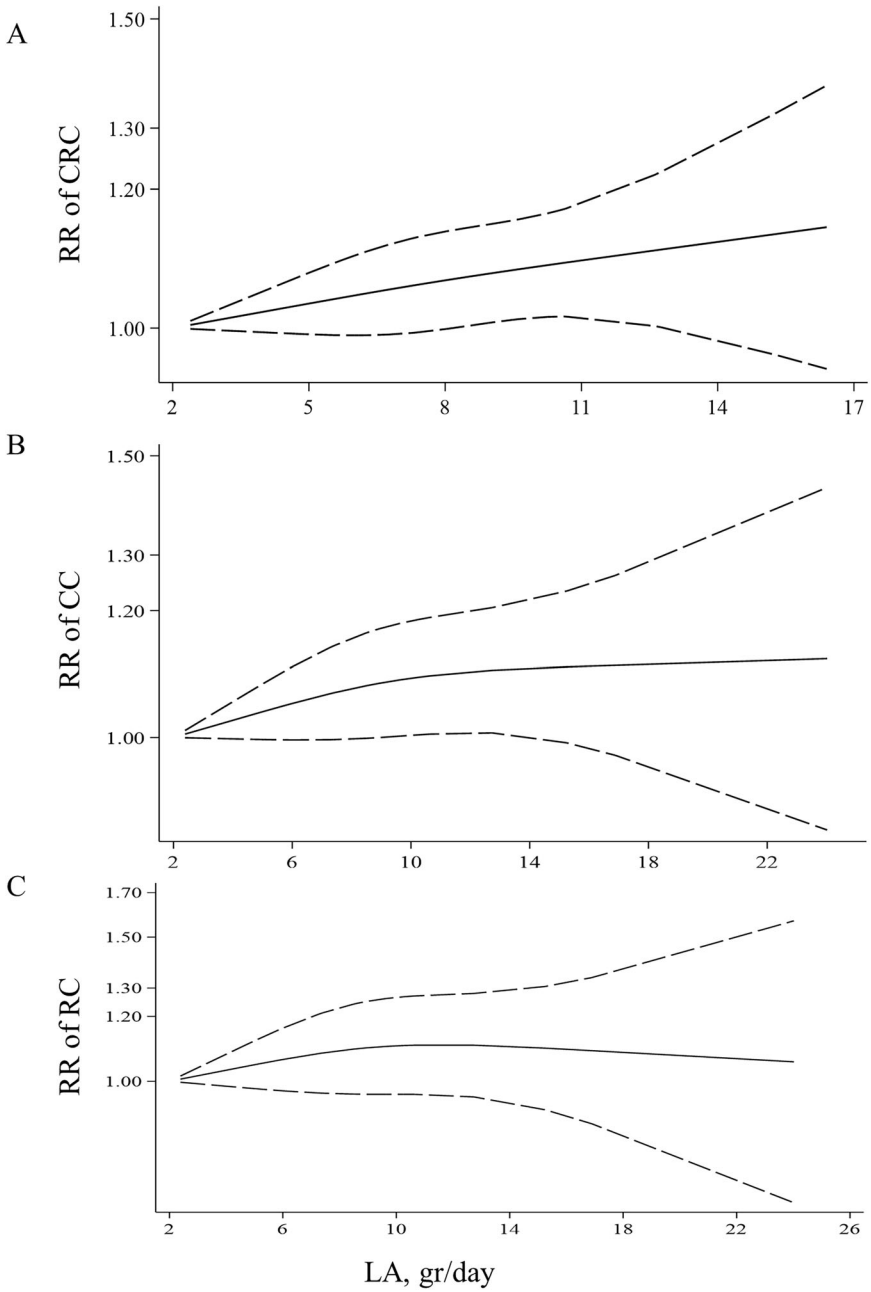

Fig. 3 Non-linear dose-response association between dietary linoleic acid and colorectal cancer in adults. A Colorectal cancer, **B** colon cancer, and **C** rectal cancer. The solid lines indicate the spline model. The dashed lines present the 95% CI. LA linoleic acid, CRC colorectal cancer, CC colon cancer, RC rectal cancer, RR relative risk.

rectal (RR: 1.35, 95% CI: 0.83–2.18, $P = 0.23$, $I^2 = 0\%$, $P = 0.84$ for heterogeneity) cancers (Table 3 and Supplementary Fig. 9). However, we found a marginally significant positive association between tissue levels of AA and colon cancer risk (RR: 1.42, 95% CI: 1.00–2.03, $P = 0.05$, $I^2 = 0\%$, $P = 0.80$ for heterogeneity). Due to the limited number of studies, we did not perform a dose-response analysis.

Subgroup and sensitivity analyses, and publication bias

Tables 1, 2, and 3 show findings from the subgroup analyses of dietary intake/tissue levels of omega-6 (total, LA, and AA) and risk of CRC and its subtypes. According to these analyses, no significant association was found between dietary intake/tissue levels of n-6 PUFAs and the risk of CRC, colon and rectal cancer in all subgroups (Table 1). However, a significant positive association was seen between dietary LA intake (for the highest versus lowest comparison) and CRC risk in men and non-US population. For rectal cancer, a significant positive association was seen with dietary LA intake in subgroups of non-US populations and high-quality studies (Table 2). For dietary intake/tissue levels of AA, we found no significant association in any subgroups (Table 3). The sensitivity analysis showed that the exclusion of any single study from the analysis did not change the pooled effect sizes significantly. According to the visual inspection of funnel plots and both Begg's test and Egger's regression, there was no significant publication bias in the associations evaluated ($P > 0.10$).

DISCUSSION

This review is, to our knowledge, the first dose-response meta-analysis exploring the associations between dietary/tissue

Table 3. Summary risk estimates for association between dietary intake (or tissue levels) of arachidonic acid and the risk of colorectal, colon, and rectal cancer in adults[a].

	No of effect sizes	Pooled relative risk (95% CI)[b]	*P*	I^2 (%)[c]	P-heterogeneity[d]
Dietary intake of AA					
The highest versus lowest comparison					
Colorectal cancer					
Overall	7	0.97 (0.86–1.10)	0.66	25.7	0.23
Subgroup analysis					
Sex					
Men	2	0.97 (0.81–1.15)	0.69	24.5	0.25
Women	4	0.96 (0.76–1.20)	0.71	49.7	0.11
Men and women	1	1.12 (0.79–1.58)	0.52	0	<0.001
Study location					
US	3	0.97 (0.84–1.13)	0.71	0	0.57
Non-US countries	4	1.00 (0.80–1.25)	0.98	56.8	0.07
Colon cancer					
Overall	5	0.97 (0.84–1.10)	0.61	0.90	0.40
Subgroup analysis					
Sex					
Men	2	1.05 (0.82–1.36)	0.68	46.7	0.17
Women	2	0.86 (0.69–1.07)	0.17	0	0.62
Men and women	1	0.98 (0.66–1.45)	0.92	0	<0.001
Study location					
US	2	1.04 (0.77–1.40)	0.82	59.2	0.12
Non-US countries	3	0.91 (0.75–1.09)	0.30	0	0.71
Rectal cancer					
Overall	5	0.89 (0.74–1.08)	0.24	0	0.74
Subgroup analysis					
Sex					
Men	2	0.83 (0.64–1.08)	0.17	0	0.90
Women	2	0.86 (0.61–1.22)	0.41	0	0.60
Men and women	1	1.18 (0.74–1.88)	0.49	0	<0.001
Study location					
US	2	0.87 (0.62–1.23)	0.43	0	0.65
Non-US countries	3	0.90 (0.71–1.14)	0.38	0	0.42
Linear dose-response association (per 100 mg/day increase)					
Colorectal cancer					
Overall	5	1.02 (0.94–1.11)	0.59	53.3	0.07
Subgroup analysis					
Sex					
Men	1	1.10 (0.94–1.29)	0.25	0	<0.001
Women	4	1.01 (0.92–1.11)	0.84	56.1	0.08
Study location					
US	3	1.02 (0.94–1.11)	0.57	0	0.37
Non-US countries	2	1.19 (0.76–1.86)	0.45	82.7	0.02
Colon cancer					
Overall	4	1.01 (0.94–1.09)	0.76	23.5	0.27
Subgroup analysis					
Sex					
Men	1	1.21 (0.98–1.49)	0.08	0	<0.001
Women	2	0.98 (0.94–1.03)	0.48	0	0.56
Men and women	1	0.95 (0.43–2.08)	0.90	0	<0.001

Table 3. continued

	No of effect sizes	Pooled relative risk (95% CI)[b]	*P*	I^2 (%)[c]	P-heterogeneity[d]
Study location					
US	2	1.09 (0.92–1.28)	0.31	46.5	0.17
Non-US countries	2	0.98 (0.94–1.03)	0.38	0	0.94
Rectal cancer					
Overall	4	0.98 (0.93–1.04)	0.52	0	0.80
Subgroup analysis					
Sex					
Men	1	0.91 (0.65–1.27)	0.58	0	<0.001
Women	2	0.98 (0.93–1.04)	0.55	0	0.60
Men and women	1	1.38 (0.54–3.50)	0.50	0	<0.001
Study location					
US	2	1.00 (0.82–1.22)	0.98	0	0.50
Non-US countries	2	0.98 (0.93–1.04)	0.51	0	0.47
Tissue levels of AA					
The highest versus lowest comparison					
Colorectal cancer					
Overall	5	0.97 (0.70–1.33)	0.83	45.8	0.12
Subgroup analysis					
Sex					
Men	1	1.16 (0.49–2.75)	0.74	0	<0.001
Women	1	0.65 (0.30–1.42)	0.28	0	<0.001
Men and women	3	1.01 (0.66–1.55)	0.96	68.1	0.04
Study quality[e]					
High quality	3	1.01 (0.66–1.55)	0.96	68.1	0.04
Low quality	2	0.84 (0.47–1.51)	0.57	0	0.33
Colon cancer					
Overall	2	1.42 (1.00–2.03)	0.05	0	0.80
Rectal cancer					
Overall	2	1.35 (0.83–2.18)	0.23	0	0.84

[a]Abbreviation: *AA* arachidonic acid, *CI* confidence interval, *US* United States.
[b]Obtained from the random effects model.
[c]Inconsistency- the percentage of variation across studies due to heterogeneity.
[d]Obtained from the *Q*-test.
[e]Studies with a median score of 7 or more, based on the NOS, were considered as a high-quality study.

biomarkers of n-6 PUFAs and risk of CRC. Our analysis revealed that higher intake of LA was associated with an increased risk of colorectal and rectal cancers. Also, in the dose-response analysis, each 1 gr/day increase in dietary LA intake was associated with a 1% higher risk of colon cancer. There was no evidence of any associations with tissue levels of LA, or dietary intake/tissue levels of n-6 PUFAs and AA.

CRC is one of the most common gastrointestinal cancers [1], with dietary factors playing an important role in its pathogenesis [50]. Of different dietary factors, n-6 PUFAs have received much attention due to their roles in inflammatory responses through the production of inflammatory prostaglandins [12]. However, findings on the association between dietary intake and tissue levels of n-6 PUFAs and CRC risk are conflicting [14, 17, 20, 31]. In this meta-analysis, we found a significant positive association between dietary LA intake and colorectal, colon, and rectal cancers. Contrary to our finding, a recent meta-analysis, conducted by Lu et al., showed no significant association between dietary LA intake and risk of CRC [33]. While this could be due to missing out some eligible studies [23, 32], Lu et al. also combined the risk estimates from cohort studies with those from case-control studies. However, our meta-analysis included only prospective studies, avoiding recall or selection biases, which could be the subject of concern in case-control studies. Similar to our findings, experimental studies have shown that high-LA and high-glucose diets increase the levels of advanced glycation end products (AGE) and the receptor of advanced glycation end products (RAGE), which are associated with CRC progression [51]. High-fat corn oil was also shown to promote colon tumorigenesis by up-regulating the cyclooxygenase-2 expression [52].

In the current meta-analysis, we found no significant association between tissue levels of LA and CRC risk. Nevertheless, a positive association was seen for dietary LA intake. The disparity might be due to LA changes during food cooking or processing. On the other hand, oils high in LA, when exposed to food processing methods such as frying and high-heat cooking, can undergo oxidation, leading to the formation of harmful compounds like lipid peroxides and aldehydes [53], which may be associated with an increased risk of CRC [54]. Moreover, a higher intake of LA, which is commonly found in vegetable oils, can lead to increased energy consumption and contribute to obesity [55], a known risk factor for CRC [56, 57]. Despite this, evidence suggests anti-cancer properties of LA levels in tissues or blood [14], indicating that dietary LA might be associated with CRC independently of tissue

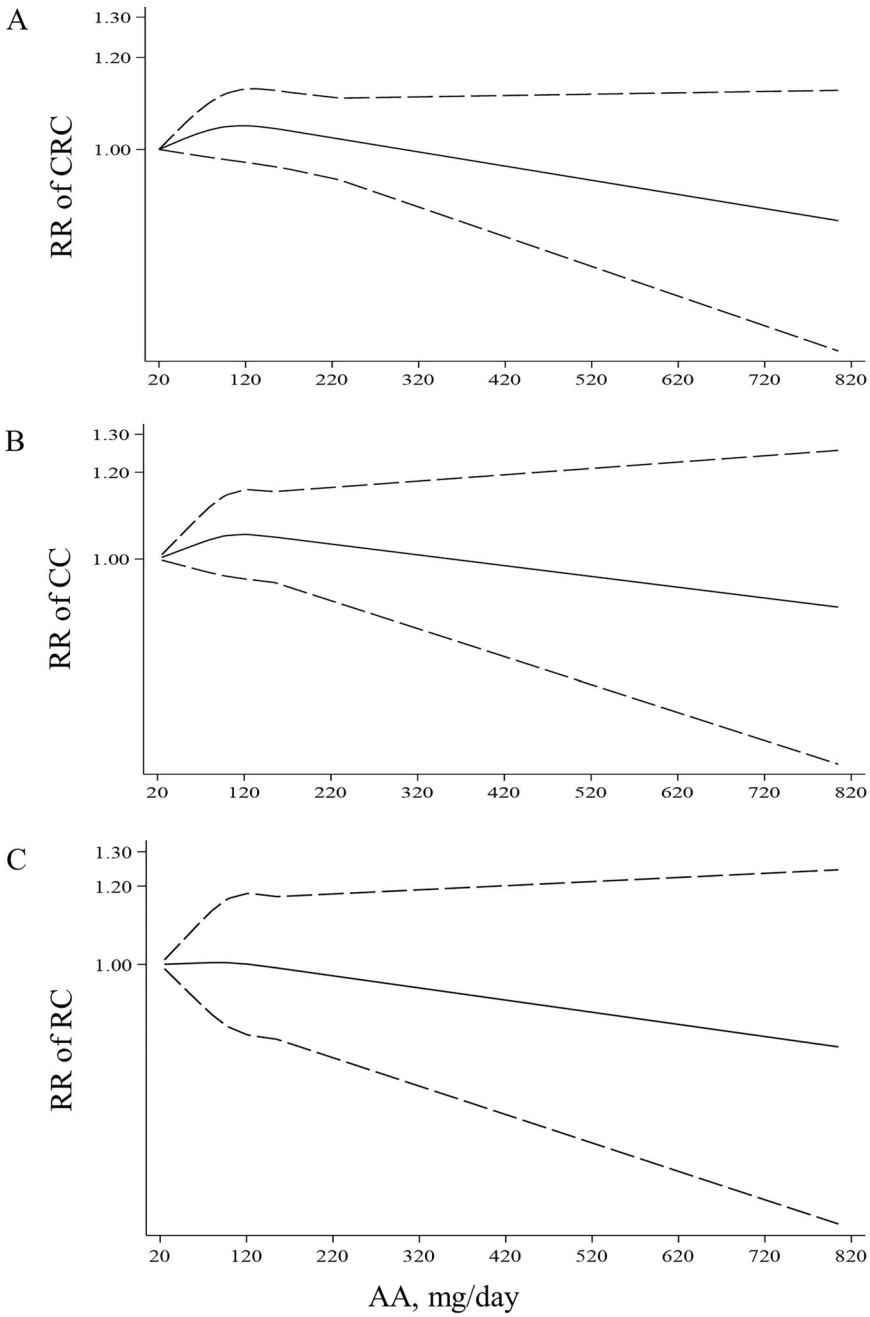

Fig. 4 Non-linear dose-response association between dietary arachidonic acid and colorectal cancer in adults. A Colorectal cancer, **B** colon cancer, and **C** rectal cancer. The solid lines indicate the spline model. The dashed lines present the 95% CI. AA arachidonic acid, CRC colorectal cancer, CC colon cancer, RC rectal cancer, RR relative risk.

LA levels. Similar to our findings, Lu et al. also reported that tissue levels of LA were not associated with CRC risk [33]. Also, it should be noted that the amount of LA in foods is low and therefore the estimation of its intake might be affected by measurement error. In addition, the positive association between dietary LA and CRC might be due to the effect of confounding variables such as other dietary factors rather than LA. Therefore, our findings on the relation between LA and CRC should be considered with caution, warranting further studies.

We found that dietary intakes of total n-6 PUFAs and AA were not associated with risk of colorectal, colon, and rectal cancers. Similarly, Lu et al. also showed no significant association between dietary intakes of total n-6 PUFAs and AA and risk of colorectal, colon, and rectal cancers [33]. The observed disparity between dietary intake of n-6 PUFAs and LA might be explained by the different effects of n-6 PUFAs (LA and long-chain n-6 PUFAs) on cancer incidence. Therefore, considering the different effects of n-6 PUFAs on cancer etiology, the cumulative effects of these fatty acids on cancer incidence might be null. For dietary intake of AA, the observed null connection may be due to AA metabolites that are produced by different pathways. Lipoxin A4 (LXA4) is produced by the lipoxygenase pathway and is considered as a tumor growth suppressor due to its anti-angiogenic properties [58]. However, PGE2 produced via the cyclooxygenase pathway plays an important role in the development of CRC [59]. Therefore, a combination of AA metabolites with different health benefits might justify the null association between dietary AA intake and risk of CRC.

Our findings should be interpreted with caution due to several limitations, most of which are common to observational studies and meta-analyses. These include being unable to perform a dose-response meta-analysis due to the limited number of studies in some associations. In addition, since the current meta-analysis was conducted on observational studies, causality cannot be established. Also, the existence of measurement and reporting errors in the estimation of food and nutrient intake is inevitable in observational studies. Moreover, previous studies have not examined the influence of processing and cooking methods or the sources of n-6 PUFAs on the association between these fatty acids and CRC risk. The source of n-6 PUFAs, whether it is derived from plant-based foods or from fast foods and snacks, may have different effects. Therefore, future studies should assess the influence of different food sources of n-6 PUFAs on CRC risk. In addition, differences in n-6 PUFAs intake among geographical regions could have affected the highest and lowest levels of n-6 PUFAs intake and the results from these comparisons. To control these differences, we conducted the subgroup and dose-response analyses.

In conclusion, we found that dietary intake of LA is associated with an increased risk of colorectal, colon, and rectal cancers. However, no significant association was found for total n-6 PUFAs and AA, either in the highest versus lowest comparison or in the dose-response meta-analysis. Also, in the dose-response analysis, each 1 gr/day increase in dietary LA intake (equal to 3.67 grams of sunflower oil, 1.6 grams of walnut oil, or 2.35 grams of pumpkin oil [60]) was associated with a 1% higher risk of colon cancer. Although the increased risk of 1% with a 1 gr/day more intake of LA might be clinically unimportant, this risk might be large in the higher dosages of LA intake. Among the studies included in the current meta-analysis, the range of LA intake was between 0 and 20 gr/day. Therefore, higher intakes of LA can provide higher risk of colon cancer. In terms of tissue levels of n-6 PUFAs, LA, and AA, no significant association was found with CRC risk. Future studies, particularly well-designed prospective cohort studies, should assess the influence of dietary/tissue levels of n-6 PUFAs on the risk of CRC mortality. Further studies are also needed to investigate whether specific foods rich in n-6 PUFAs are differentially associated with CRC risk.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

NA contributed to the literature search. NA and NE contributed to data extraction and data analysis. NA and OS drafted the manuscript which was critically revised for important intellectual content by all authors. MA contributed to the manuscript editing and obtained funding. JAS and GA contributed to the manuscript editing. OS supervised the study. All authors have read and approved the final manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All analyses were based on previously published studies; thus, no ethical approval is required.

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