Gut and Liver
https://doi.org/10.5009/gnl250104
pISSN 1976-2283 eISSN 2005-1212

Original Article

Dietary β-Carotene, Vitamin A, and Retinol Intake and Prevalence of Colorectal Adenoma: A Cross-Sectional Study and Meta-Analysis

Joowon Chung[1], Jioh Kang[2], Sang Hoon Kim[3], Min Kyu Jung[4], Dong Hyun Kim[5], Hyun Joo Song[6], Ki Bae Kim[7], Seung-Joo Nam[8], Hoon Jai Chun[9], Jung Eun Lee[2,10], Yun Jeong Lim[11], Korean GI Nutrition Study Group (K-GINUS)

[1]Department of Internal Medicine, Nowon Eulji Medical Center, Eulji University School of Medicine, Seoul, Korea; [2]Department of Food and Nutrition, College of Human Ecology, Seoul National University, Seoul, Korea; [3]Division of Gastroenterology, Department of Internal Medicine, Chung-Ang University Gwangmyeong Hospital, Gwangmyeong, Korea; [4]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Kyungpook National University Hospital, Daegu, Korea; [5]Department of Internal Medicine, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Korea; [6]Department of Internal Medicine, Jeju National University College of Medicine, Jeju, Korea; [7]Department of Internal Medicine, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, Korea; [8]Department of Internal Medicine, Kangwon National University School of Medicine, Chuncheon, Korea; [9]Department of Internal Medicine, Institute of Gastrointestinal Medical Instrument Research, Korea University College of Medicine, Seoul, Korea; [10]Research Institute of Human Ecology, Seoul National University, Seoul, Korea; [11]Department of Internal Medicine, Dongguk University Ilsan Hospital, Dongguk University, College of Medicine, Goyang, Korea

Article Info

Received March 1, 2025
Revised May 6, 2025
Accepted May 19, 2025

Corresponding Author

Yun Jeong Lim
ORCID https://orcid.org/0000-0002-3279-332X
E-mail drlimyj@gmail.com

Background/Aims: Antioxidants may offer protection against colorectal cancer, but their association with colorectal adenomas remains unclear due to variations in study design, population, and dietary factors. We investigated the relationship between dietary intake of β-carotene, vitamin A, and retinol and the prevalence of colorectal adenoma using food frequency questionnaires (FFQs) and colonoscopy data.

Methods: We recruited participants undergoing elective colonoscopy across eight medical institutions. FFQs were administered prior to colonoscopy, and nutrient intakes were categorized into quartiles. Multivariate logistic regression was used to estimate odds ratios (ORs) adjusting for potential cofounders. A meta-analysis of 11 observational studies, including our own, was also conducted.

Results: Among 720 eligible participants (mean age 52.44±14.30 years; body mass index 23.82±3.46 kg/m^2), colorectal adenoma was identified in 266 (36.9%). Higher intake of β-carotene and vitamin A was associated with a significantly lower prevalence of colorectal adenoma (p for trend <0.05). Adjusted ORs for the highest versus lowest quartile were 0.43 (95% confidence interval [CI], 0.20 to 0.91) for β-carotene and 0.34 (95% CI, 0.15 to 0.76) for vitamin A. Conversely, higher retinol intake was linked to increased adenoma prevalence (OR, 2.16; 95% CI, 1.09 to 4.29), particularly among individuals with high-fat diets. Meta-analysis confirmed a protective association for β-carotene (OR, 0.60; 95% CI, 0.46 to 0.78), but not for vitamin A or retinol.

Conclusions: We demonstrated an inverse association between β-carotene and colorectal adenoma prevalence, whereas the effects of vitamin A and retinol appeared to vary depending on dietary context. These findings highlight the complex influence of dietary pattern and nutrient sources on colorectal adenoma risk. **(Gut Liver, Published online August 8, 2025)**

Key Words: Antioxidants; β-Carotene; Vitamin A; Retinol; Colorectal adenoma

INTRODUCTION

The colorectal adenoma-carcinoma sequence is a well-established pathway of colorectal carcinogenesis, in which oxidative is thought to play a significant role.[1] Oxidative stress arises when the production of free radicals and

reactive oxygen species exceeds the cellular antioxidant defense capacity.[2] Excess reactive oxygen species can damage genomic and mitochondrial DNA, induce molecular mutations, and dysregulate key signaling pathways.[3] These changes may promote abnormal cellular proliferation and contribute to the initiation and progression of colorectal adenoma.

Antioxidants, which neutralize free radicals, and mitigate oxidative damage, have garnered attention, as potential chemopreventive agents. Fruits, vegetables, and whole grains are major dietary sources of dietary antioxidants, such as β-carotene, vitamin A, vitamin C, vitamin E, and selenium. Accordingly, dietary antioxidant intake has been proposed as a strategy to reduce cellular damage, and modulate immune function, and potentially suppress the development of colorectal neoplasia.[4-6]

Since the 1980s, numerous epidemiological studies have explored the role of antioxidants in gastrointestinal cancer prevention.[7-9] Observational and experimental studies, including case-control studies, cohort, and randomized controlled trials, have reported mixed outcomes,[10-15] and meta-analyses have not conclusively established their effectiveness.[16-18] These inconsistencies arise from population differences, dietary variations, supplement use, and study designs, leading to substantial heterogeneity. In particular, research on antioxidant intake and colorectal adenomas, which are precursor lesions to cancer, is relatively limited. Moreover, many studies rely on self-reported cancer screening outcomes rather than colonoscopy-confirmed diagnoses, which may reduce accuracy.

In this study, we investigated the associations between dietary intake of β-carotene, vitamin A, and retinol and the prevalence of colorectal adenomas, using data from self-reported food frequency questionnaires (FFQs) administered prior to colonoscopy. In addition, we conducted a meta-analysis incorporating case-control and cohort studies to contextualize our findings. This integrated approach aims to clarify the role of specific antioxidant nutrients in colorectal adenoma prevention and inform future dietary recommendations.

MATERIALS AND METHODS

1. Study design and participants

This study included participants who underwent gastrointestinal endoscopy at eight hospitals in Korea (July 2021 to October 2023). Participants, aged ≥19, were asked to complete a detailed questionnaire on demographics, medical history, lifestyle, and dietary intake before elective endoscopy. We excluded individuals with missing information on colorectal adenoma diagnosis (n=377) or those diagnosed with colorectal cancer (n=19). Additionally, participants with missing FFQ data (n=11), or implausible energy intake (≤360.1 kcal/day or ≥9,290 kcal/day, corresponding to more than 3 standard deviations above or below the mean of the log-transformed energy intake) (n=15) were excluded. After these exclusions, a total of 720 participants were included in the analysis (Fig. 1). This study shares part of the participant cohort with our previous study examining dietary calcium intake and colorectal adenoma risk.[19] This study was approved by the Institutional Review Board of each hospital; Chonnam National University Hospital (CNUH-2021-250), Chungnam National University Sejong Hospital (CNUSH 2021-08-002), Donguk University Hospital (DUIH 2021-03-030-005), Kyungpook National University Hospital (KNUH 2021-05-011), Chungbuk National University Hospital (CBNUH 2021-07-027-001), Kangwon National University Hospital (KNUH-A-2021-05-011-012), Eulji University Hospital (EMCS 2022-12-015), and Jeju National University Hospital (2021-06-005). All subjects participated voluntarily and provide informed consent.

2. FFQ-assessment of β-carotene, vitamin A, and retinol intake

Dietary intake of β-carotene, vitamin A, and retinol were assessed using a validated semiquantitative 113-item FFQ, developed for the Korean population by the Korea National Health and Nutrition Examination Survey Team of the Korean Centers for Disease Control and Prevention based on 1-day 24-hour data collected from adults aged >19 years in the fourth Korea National Health and Nutri-

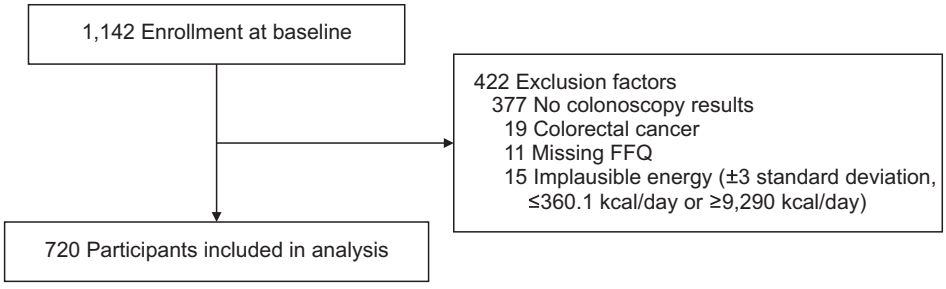

Fig. 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram for subjects of this study. FFQ, food frequency questionnaire.

tion Examination Survey (2007 to 2009).[20] The validation and reliability of the FFQ have been previously described.[21] Participants reported the frequency and quantity of each food item consumed over the past year. Dietary intake was calculated by multiplying consumption frequency by portion size and nutrient content from the eighth edition Korean Food Composition Table.[22] To distinguish between performed vitamin A (retinol) and provitamin A carotenoids (such as β-carotene), each nutrient was analyzed separately using data from the Korean Food Composition Table.

1) Data analysis

(1) Assessment of covariates

Participants completed a structured questionnaire on sociodemographic, lifestyle, and clinical characteristics, including age, sex, education, smoking status, physical activity, colon polyp history, hypertension, diabetes, and aspirin use. Smoking history included smoking status, pack-years, age at initiation, and age at cessation. Physical activity was assessed using metabolic equivalent of tasks (METs) hours per week.[23] Body mass index was calculated from height and weight measured at each hospital. Diabetes and hypertension were defined based on a self-reported diagnosis or medication use. Alcohol intake (g/day) was estimated from ethanol content in beer, soju, wine, and rice wine over the past year.

(2) Ascertainment of colorectal adenomas

Colorectal adenomas were confirmed by trained gastroenterologists through colonoscopy and histopathology. Anatomic subsites were classified as proximal (cecum, ascending, and transverse colon) and distal (descending, sigmoid colon, and rectum). Due to the limited rectal adenoma cases (n=9), they were merged with the distal group. Advanced adenomas were defined as lesions with villous components, a diameter of ≥10 mm, or the presence of high-grade dysplasia.

(3) Statistical analysis

Dietary intakes of β-carotene, vitamin A, and retinol were energy-adjusted using the residual model.[24] Odds ratio (OR) and 95% confidence intervals (CIs) were calculated using multivariate logistic regression models to assess the association with the colorectal adenoma prevalence. Participants were categorized into quartiles, and trend tests used median quartile values as continuous variables.

Multivariate logistic regression models were adjusted for the covariates described above, including demographic, lifestyle, and dietary factors. Additional adjustments were made for dietary calcium and fiber intake. Missing pack-years (7% past smokers, 1% current smokers) were handled separately, and other missing categorical values (<5%) were imputed using the modal category. Subgroup analyses were conducted by colorectal subsite (proximal vs distal), red/processed meat intake, and total fat intake to assess effect modification.

Vitamin A intake was primarily analyzed in retinol equivalents (RE; μgRE/day), and sensitivity analyses using retinal activity equivalents (RAE) were conducted to account for differences in bioavailability across vitamin A sources. The conversion was performed using the formula to account for bioavailability differences:[25]

$$\text{Vitamin A } (\mu g \text{ RAE}) = \text{retinol } (\mu g) + (\beta\text{-carotene } (\mu g)/12) + (\text{other provitamin A carotenoids } (\mu g)/24).$$

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA), and two-sided p-values of <0.05 were considered statistically significant.

2) Meta-analysis

(1) Data sources and searches

A structured search of PubMed was conducted by two independent investigators (J.C. and J.K.) for studies published between January 1, 1991, and December 31, 2023. To ensure reliability, two blinded assessors independently evaluated study quality, unaware of study outcomes or authorship. Stratified analyses and meta-regression assessed study design, sample size, and geographic region to address heterogeneity.

Studies were identified using Medical Subject Headings (MeSH) and keywords based on the following two search strategies. The first strategy included: (1) β-carotene or vitamin A or retinol; (2) adenoma or polyp or polyps; and (3) colorectal or colon or rectal or colorectum or large bowel. The second strategy included: (1) antioxidant or micronutrient or nutrient or nutritional; (2) adenoma or polyp or polyps; and (3) colorectal or colon or rectal or colorectum or large bowel. Additionally, reference lists of relevant articles were reviewed for further studies.

(2) Study selection and quality assessment

Studies on the association between dietary intake of β-carotene, vitamin A, and retinol and colorectal adenoma were included if they: (1) had a case-control or cohort design, and (2) reported OR or relative risk (RR) estimates with 95% CIs. Excluded studies included animal and molecular/genetic studies, and clinical studies assessing only supplemental intake, reporting only blood/tissue levels, lacking variability measures, or not written in English. Two reviewers independently extracted key study data, in-

cluding design, population, sample size, dietary exposure, outcomes, and risk estimates, using a standardized form. Study quality was assessed using the Newcastle-Ottawa Scale,[26] and discrepancies were resolved by consensus.

(3) Data extraction

Data extracted from the articles included: first author, published year, country, study design, sex, sample size (cases/controls or total participants), endpoint (first adenoma, recurrent adenoma, or both), nutrient type, fully adjusted ORs or RRs (95% CIs) for the highest versus lowest intake group, and adjusted covariates. For studies reporting both hospital-based and population-based controls, population-based data were used.[27] Studies with separate results for first and recurrent adenoma were treated independently, as participant groups differed.[28] The meta-analysis was performed in accordance with the Meta-analysis of Observational Studies in Epidemiology guidelines.[29]

(4) Statistical analysis

We used a random-effects model (DerSimonian & Laird) to calculate RRs and 95% CIs for colorectal adenoma.[30] Q and I^2 statistics assessed heterogeneity, with study weights assigned inversely to variance. For sensitivity analyses, we examined studies focusing on either first-occurrence or recurrent adenoma. Publication bias was evaluated using Egger's regression asymmetry test and funnel plot, but only for dietary β-carotene and vitamin A due to the limited number of retinol studies. We conducted subgroup analyses by geographic region (North America, Europe, Asia) and meta-regression to explore regional effects. All statistical analyses were performed using the R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) with the software package 'meta.'[31] Two-sided p values of less than 0.05 were considered statistically significant.

RESULTS

The study included 392 men and 328 women, with a mean age of 52.44±14.30 years and a mean body mass index of 23.82±3.46 kg/m^2. Colorectal adenoma was detected in 266 participants. While all participants met the recommended β-carotene intake (430 to 7,000 μg), the reference group (1st quartile) had vitamin A intake below the recommended range (500 to 3,000 μg).[25] Baseline characteristics of this study population are presented in Table 1. Supplementary Tables 1-3 provide detailed characteristics stratified by quartiles of dietary β-carotene, vitamin A, and retinol intake, respectively.

Table 2 shows the prevalence of colorectal adenoma by quartiles of dietary β-carotene, vitamin A, and retinol intake, adjusted for covariates. Model 1 adjusted for age, sex, and total energy intake. Model 2 further adjusted for study center, body mass index, smoking status, physical activities, educational level, history of colon polyp resection, years since last colonoscopy, hypertension, diabetes, aspirin use, and family history of colorectal cancer. Model 3 additionally adjusted for dietary calcium and dietary fiber intake.

Higher dietary intake of β-carotene and vitamin A was significantly associated with lower colorectal adenoma prevalence (p for trend <0.05 in all models). In contrast, higher retinol intake was associated with an increased prevalence of colorectal adenoma. In Model 3, participants in the highest quartile of β-carotene and vitamin A intake

Table 1. Baseline Characteristics of Participants

Characteristic	Total (n=720)
Age, yr	52.44±14.30
BMI, kg/m^2	23.82±3.46
Physical activity (MET-hours/wk)	23.42±33.34
Sex	
Male	392 (54.4)
Female	328 (45.6)
Education level	
Below high school	103 (14.3)
High school	273 (37.9)
College or more	341 (47.4)
Missing	3 (0.4)
Smoking status	
Never	409 (56.8)
Past	191 (26.5)
Current	119 (16.5)
Missing	1 (0.1)
History of colon polyp resection	
Never	376 (52.2)
≤2 yr	160 (22.2)
>2 to 4 yr	91 (12.6)
>4 yr	86 (11.9)
Missing	7 (1.0)
Years since last colonoscopy	
First time	178 (24.7)
≤1 yr	224 (31.1)
>1 to 3 yr	166 (23.1)
>3 yr	149 (20.7)
Missing	3 (0.4)
Family history of colorectal cancer	
Yes	90 (12.5)
No	627 (87.1)
Missing	3 (0.4)
Hypertension	212 (29.4)
Diabetes	106 (14.7)
Taking aspirin	42 (5.8)

Data are presented as mean±SD or number (%).
BMI, body mass index; MET, metabolic equivalent task.

Table 2. Associations between Dietary Intake of β-Carotene, Vitamin A and Retinol and Colorectal Adenoma

	Quartile 1 (n=180)	Quartile 2 (n=180)	Quartile 3 (n=180)	Quartile 4 (n=180)	p for trend
β-Carotene					
No. of cases	76	67	59	64	
Median (IQR), μg/day	1,451 (1,115–1,688)	2,281 (2,104–2,477)	3,101 (2,876–3,372)	4,711 (4,078–5,860)	
Model 1	1	0.82 (0.52–1.31)	0.62 (0.39–1.00)	0.58 (0.35–0.94)	0.02
Model 2	1	0.93 (0.55–1.54)	0.69 (0.41–1.18)	0.61 (0.35–1.05)	0.05
Model 3	1	0.74 (0.41–1.31)	0.49 (0.25–0.95)	0.43 (0.20–0.91)	0.03
Vitamin A					
No. of cases	82	64	57	63	
Median (IQR), μgRE/day	341.1 (271.5–395.8)	504.5 (460.2–532.1)	654.3 (611.3–699.1)	929.0 (824.4–1,142.3)	
Model 1	1	0.66 (0.42–1.05)	0.55 (0.34–0.88)	0.52 (0.32–0.85)	0.01
Model 2	1	0.77 (0.47–1.29)	0.59 (0.35–1.00)	0.58 (0.33–1.00)	0.04
Model 3	1	0.55 (0.30–1.00)	0.36 (0.18–0.72)	0.34 (0.15–0.76)	0.02
Retinol					
No. of cases	72	69	60	65	
Median (IQR), μg/day	48.7 (36.9–58.3)	79.6 (73.0–86.9)	108.4 (101.6–116.6)	166.2 (144.2–201.8)	
Model 1	1	1.29 (0.81–2.06)	1.13 (0.70–1.81)	1.22 (0.76–1.94)	0.55
Model 2	1	1.37 (0.83–2.28)	1.27 (0.77–2.10)	1.50 (0.90–2.52)	0.17
Model 3	1	1.58 (0.92–2.70)	1.69 (0.94–3.05)	2.16 (1.09–4.29)	0.04

Data are presented as odds ratio (95% confidence interval).
Model 1 was adjusted for age (years, continuous), sex (male, female), and total energy intake (kcal/day, continuous). Model 2 was further adjusted for center, body mass index (kg/m^2, continuous), smoking status (never, past smoker with ≤18.4 pack-years, past smoker with >18.4 pack-years, past smoker with missing pack-years, current smoker with ≤16.5 pack-years, current smoker with >16.5 pack-years), physical activities (MET-hours/week, continuous), educational level (below high school, high school, college or more), alcohol intake (g/day, continuous), history of colon polyp resection (never, ≤2 years, >2 to ≤4 years, and >4 years), years since most recent colonoscopy (first time, ≤1 year, >1 to ≤3 years, and >3 years), hypertension (yes, no), diabetes (yes, no), taking aspirin (yes, no), and family history of colorectal cancer (yes, no). Model 3 was further adjusted for variables listed in Model 2 and dietary calcium intake (quartiles), dietary fiber intake (quartiles).
IQR, interquartile range; RE, retinol equivalents; MET, metabolic equivalent task.

showed 57% and 66% lower prevalence of adenoma, respectively, compared to the lowest quartile (p for trend 0.03 and 0.02). Retinol intake was associated with more than a two-fold increase in prevalence in the highest quartile (p for trend 0.04). The inverse association for β-carotene and vitamin A intake were most pronounced in the distal colon and rectum, whereas no significant associations were found in the proximal colon (Supplementary Table 4).

1. Interaction between nutrient and red meat intake on colorectal adenoma prevalence

Table 3 presents the association between nutrient intake and colorectal adenoma prevalence stratified by red meat consumption. No statistically significant interactions were observed (p for interaction>0.05). However, the inverse associations of β-carotene and vitamin A intake with adenoma prevalence appeared stronger among participants with higher red meat consumption (>62 g/day), with significant trends observed in fully adjusted models (p for trend=0.05 and p for trend=0.02, respectively). In contrast, retinol intake showed a positive trend in adenoma prevalence in the high red meat group, although this did not reach statistical significance.

2. Interaction between nutrient and fat intake on colorectal adenoma prevalence

Table 4 presents the interaction between nutrient intake and dietary fat intake. Although β-carotene and vitamin A intake were associated with a decreasing trend in adenoma prevalence in both high-fat (>46 g/day) and low-fat (≤46 g/day) groups, the interactions were not statistically significant (p for interaction>0.05). Notably, retinol intake showed a significant positive association with adenoma prevalence in the high-fat intake group (p for trend=0.01), suggesting that a high-fat diet may potentiate the risk associated with higher retinol consumption.

3. Meta-analysis

The literature search yielded 392 citations: 286 from keyword group 1 and 106 from keyword group 2. After initial screening, 32 papers were selected, with four additional studies identified through manual searching. Following removal of duplicates (n=9) and exclusion of irrelevant studies (n=16), a total of 12 studies–including our own–were included in the meta-analysis (Fig. 2). Specifically, eight studies reported on β-carotene intake,[32-38] eight on vitamin A,[27,32-34,36,39,40] and five on retinol.[35,36,38,41] Our study contributed data to all three analyses (Table 5). The quality assessment for each included study is summarized in

Table 3. Subgroup Analyses for the Associations between Dietary Intake of β-Carotene, Vitamin A and Retinol and Colorectal Adenoma based on Red and Processed Meat Consumption*

Nutrient	Subgroup	Quartile 1 (n=180)	Quartile 2 (n=180)	Quartile 3 (n=180)	Quartile 4 (n=180)	p for trend	p for interaction
β-Carotene	Median (IQR), μg/day	1,451 (1,115–1,688)	2,281 (2,104–2,477)	3,101 (2,876–3,372)	4,711 (4,078–5,860)		
	Higher red meat intake (>62 g, median)						
	No. of cases/total	27/77	35/100	34/104	26/79		0.77
	Model 1	1	0.88 (0.43–1.77)	0.67 (0.32–1.37)	0.60 (0.27–1.33)	0.17	
	Model 2	1	0.90 (0.41–1.99)	0.65 (0.29–1.47)	0.56 (0.23–1.34)	0.15	
	Model 3	1	0.49 (0.19–1.27)	0.28 (0.09–0.84)	0.24 (0.07–0.84)	0.05	
	Lower red meat intake (≤62 g, median)						
	No. of cases/total	49/103	32/80	25/76	38/101	49/103	
	Model 1	1	0.77 (0.41–1.44)	0.55 (0.28–1.06)	0.56 (0.30–1.05)	0.06	
	Model 2	1	0.81 (0.38–1.71)	0.53 (0.24–1.17)	0.51 (0.24–1.07)	0.07	
	Model 3	1	0.77 (0.34–1.74)	0.49 (0.19–1.23)	0.42 (0.15–1.18)	0.10	
Vitamin A	Median (IQR), μgRE/day	341.1 (271.5–395.8)	504.5 (460.2–532.1)	654.3 (611.3–699.1)	929.0 (824.4–1,142)		
	Higher red meat intake (>62 g, median)						
	No. of cases/total	31/73	32/101	33/102	26/84		0.94
	Model 1	1	0.48 (0.23–0.99)	0.53 (0.26–1.09)	0.41 (0.18–0.92)	0.07	
	Model 2	1	0.55 (0.25–1.22)	0.53 (0.22–1.21)	0.41 (0.17–1.01)	0.08	
	Model 3	1	0.27 (0.10–0.73)	0.21 (0.07–0.64)	0.14 (0.04–0.56)	0.02	
	Lower red meat intake (≤62 g, median)						
	No. of cases/total	51/107	32/79	24/78	37/96		
	Model 1	1	0.81 (0.43–1.51)	0.50 (0.26–0.97)	0.59 (0.31–1.11)	0.07	
	Model 2	1	0.91 (0.44–1.90)	0.48 (0.22–1.04)	0.59 (0.28–1.24)	0.11	
	Model 3	1	0.87 (0.37–2.06)	0.39 (0.14–1.06)	0.45 (0.15–1.36)	0.15	
Retinol	Median (IQR), μg/day	48.7 (36.9–58.3)	79.6 (73.0–86.9)	108.4 (101.6–116.6)	166.2 (144.2–201.8)		
	Higher red meat intake (>62 g, median)						
	No. of cases/total	27/68	34/103	33/105	28/84		0.82
	Model 1	1	1.03 (0.51–2.10)	1.05 (0.51–2.17)	1.19 (0.56–2.53)	0.63	
	Model 2	1	1.13 (0.51–2.49)	1.35 (0.61–2.99)	1.77 (0.74–4.24)	0.17	
	Model 3	1	1.44 (0.61–3.40)	2.28 (0.88–5.94)	3.46 (1.12–10.70)	0.03	
	Lower red meat intake (≤62 g, median)						
	No. of cases/total	45/112	35/77	27/75	37/96		
	Model 1	1	1.57 (0.84–2.94)	1.14 (0.60–2.17)	1.21(0.67–2.21)	0.71	
	Model 2	1	1.82 (0.89–3.74)	1.22 (0.60–2.50)	1.46 (0.73–2.91)	0.44	
	Model 3	1	2.27 (1.06–4.86)	1.63 (0.71–3.72)	1.98 (0.77–5.09)	0.23	

Data are presented as odds ratio (95% confidence interval).

Model 1 was adjusted for center, age (years, continuous), sex (male, female), and total energy intake (kcal/day, continuous). Model 2 was further adjusted for body mass index (kg/m^2, continuous), smoking status (never, past smoker with ≤18.4 pack-years, past smoker with >18.4 pack-years, past smoker with missing pack-years, current smoker with ≤16.5 pack-years, current smoker with >16.5 pack-years), physical activities (MET-hours/week, continuous), educational level (below high school, high school, college or more), alcohol intake (g/day, continuous), history of colon polyp resection (never, ≤2 years, >2 to ≤4 years, and >4 years), years since most recent colonoscopy (first time, ≤1 year, >1 to ≤3 years, and >3 years), hypertension (yes, no), diabetes (yes, no), taking aspirin (yes, no), and family history of colorectal cancer (yes, no). Model 3 was further adjusted for variables listed in Model 2 and dietary calcium intake (quartiles), dietary fiber intake (quartiles).

IQR, interquartile range; RE, retinol equivalents; MET, metabolic equivalent task.

*Red meat includes beef, pork, its offal, and processed meat includes sausage, bacon and ham.

Table 4. Subgroup Analyses for the Associations between Dietary Intake of β-Carotene, Vitamin A and Retinol and Colorectal Adenoma based on Total Fat Consumption

Nutrient	Subgroup	Quartile 1 (n=180)	Quartile 2 (n=180)	Quartile 3 (n=180)	Quartile 4 (n=180)	p for trend	p for interaction
β-Carotene	Median (IQR), μg/day	1,451 (1,115–1,688)	2,281 (2,104–2,477)	3,101 (2,876–3,372)	4,711 (4,078–5,860)		
	Higher fat intake (>46 g, median)						
	No. of cases/total	14/55	26/88	30/105	37/112		0.92
	Model 1	1	1.04 (0.44–2.47)	0.68 (0.29–1.62)	0.61 (0.25–1.48)	0.16	
	Model 2	1	1.27 (0.49–3.30)	0.74 (0.28–1.94)	0.63 (0.23–1.69)	0.15	
	Model 3	1	0.93 (0.30–2.90)	0.46 (0.13–1.59)	0.35 (0.09–1.38)	0.07	
	Lower fat intake (≤46 g, median)						
	No. of cases/total	62/125	41/92	29/75	27/68		
	Model 1	1	0.85 (0.47–1.51)	0.67 (0.36–1.24)	0.62 (0.32–1.19)	0.12	
	Model 2	1	0.97 (0.49–1.92)	0.76 (0.37–1.57)	0.76 (0.35–1.66)	0.41	
	Model 3	1	0.76 (0.36–1.61)	0.53 (0.22–1.31)	0.52 (0.19–1.48)	0.21	
Vitamin A	Median (IQR), μgRE/day	341.1 (271.5–395.8)	504.5 (460.2–532.1)	654.3 (611.3–699.1)	929.0 (824.4–1,142)		
	Higher fat intake (>46 g, median)						
	No. of cases/total	15/46	24/82	29/111	39/121		0.26
	Model 1	1	0.65 (0.26–1.60)	0.40 (0.16–0.98)	0.38 (0.15–0.96)	0.05	
	Model 2	1	0.71 (0.26–1.96)	0.43 (0.16–1.16)	0.35 (0.12–1.01)	0.04	
	Model 3	1	0.46 (0.14–1.56)	0.18 (0.05–0.72)	0.11 (0.02–0.55)	0.01	
	Lower fat intake (≤46 g, median)						
	No. of cases/total	67/134	40/98	28/69	24/59		
	Model 1	1	0.69 (0.39–1.20)	0.74 (0.39–1.38)	0.64 (0.32–1.27)	0.21	
	Model 2	1	0.94 (0.48–1.85)	0.80 (0.39–1.66)	1.06 (0.47–2.42)	0.97	
	Model 3	1	0.66 (0.30–1.48)	0.57 (0.22–1.49)	0.79 (0.25–2.47)	0.72	
Retinol	Median (IQR), μg/day	48.7 (36.9–58.3)	79.6 (73.0–86.9)	108.4 (101.6–116.6)	166.2 (144.2–201.8)		
	Higher fat intake (>46 g, median)						
	No. of cases/total	10/32	20/75	32/112	45/141		0.75
	Model 1	1	0.91 (0.34–2.42)	1.05 (0.41–2.65)	1.20 (0.49–2.96)	0.46	
	Model 2	1	0.82 (0.28–2.44)	1.35 (0.49–3.70)	1.46 (0.54–4.00)	0.22	
	Model 3	1	1.16 (0.37–3.64)	2.23 (0.71–6.94)	2.80 (0.80–9.74)	0.07	
	Lower fat intake (≤46 g, median)						
	No. of cases/total	62/148	49/105	28/68	20/39		
	Model 1	1	1.59 (0.92–2.74)	1.35 (0.72–2.51)	1.79 (0.84–3.80)	0.12	
	Model 2	1	1.77 (0.94–3.34)	1.60 (0.78–3.31)	2.36 (0.97–5.73)	0.04	
	Model 3	1	1.85 (0.92–3.70)	2.03 (0.87–4.73)	2.83 (0.95–8.45)	0.05	

Data are presented as odds ratio (95% confidence interval).

Model 1 was adjusted for age (years, continuous), sex (male, female), and total energy intake (kcal/day, continuous). Model 2 was further adjusted for center, body mass index (kg/m^2, continuous), smoking status (never, past smoker with ≤18.4 pack-years, past smoker with >18.4 pack-years, past smoker with missing pack-years, current smoker with ≤16.5 pack-years, current smoker with >16.5 pack-years), physical activities (MET-hours/week, continuous), educational level (below high school, high school, college or more), alcohol intake (gay/day, continuous), history of colon polyp resection (never, ≤2 years, >2 to ≤4 years, and >4 years), years since most recent colonoscopy (first time, ≤1 year, >1 to ≤3 years, and >3 years), hypertension (yes, no), diabetes (yes, no), taking aspirin (yes, no), and family history of colorectal cancer (yes, no). Model 3 was further adjusted for variables listed in Model 2 and dietary calcium intake (quartiles), dietary fiber intake (quartiles).

IQR, interquartile range; RE, retinol equivalents; MET, metabolic equivalent task.

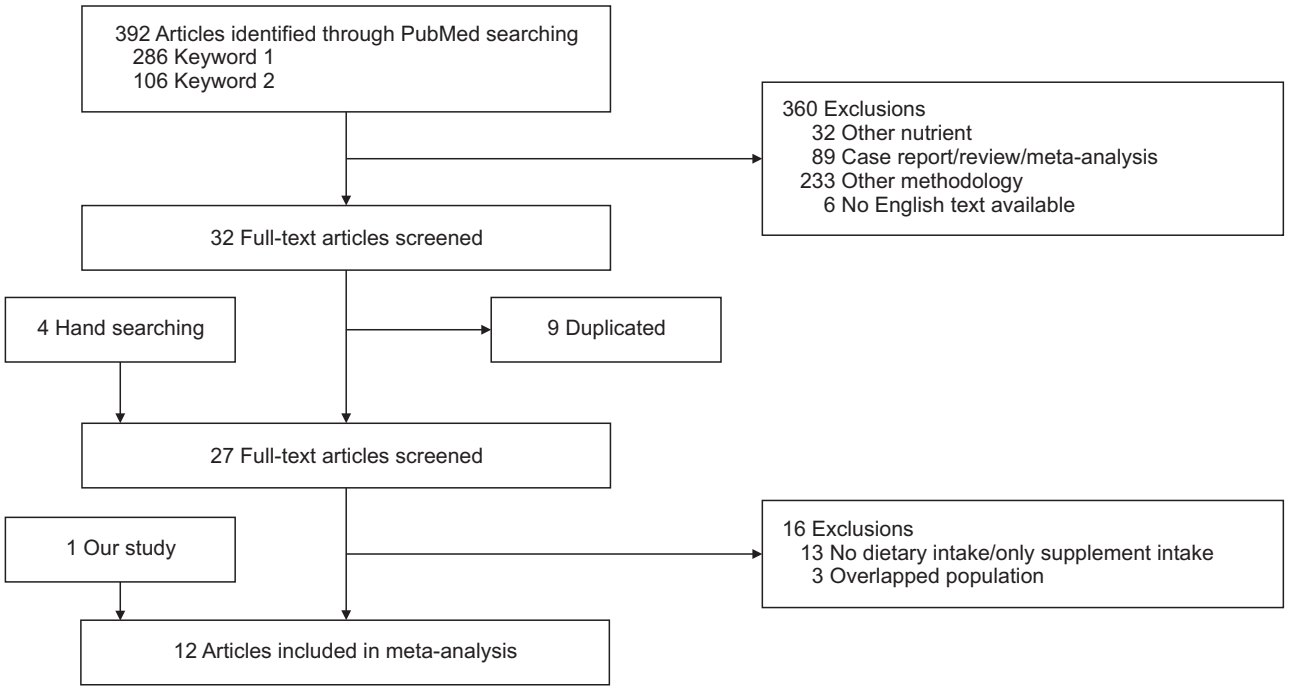

Fig. 2. Flow diagram of the systematic literature search on the relationship between the risk of colorectal adenoma and dietary β-carotene, vitamin A, and retinol intake.

Supplementary Table 5.

The pooled analysis demonstrated that higher β-carotene intake was significantly associated with a lower prevalence of colorectal adenoma, with a pooled RR of 0.60 (95% CI, 0.46 to 0.78), accompanied by moderate heterogeneity (I^2=56%, p=0.03) (Table 6, Fig. 3). The protective effect was more pronounced in studies conducted in Asian (RR, 0.32; 95% CI, 0.18 to 0.58) and North American populations (RR, 0.72; 95% CI, 0.65 to 0.81), with no heterogeneity observed within these regions (Table 6, Fig. 4). In contrast, studies from Europe reported a pooled RR of 0.45 (95% CI, 0.14 to 1.48) with substantial heterogeneity (I^2=86%, p<0.01), suggesting regional variability. Meta-regression analysis indicated a marginally significant regional interaction (p for interaction=0.06) for β-carotene intake.

For dietary vitamin A intake, the pooled RR was 0.79 (95% CI, 0.53 to 1.17), indicating no significant association with colorectal adenoma risk. However, substantial heterogeneity was observed across studies (I^2=72%, p<0.01) (Table 6, Fig. 5). Regional subgroup analyses showed pooled RR of 0.82 (95% CI, 0.36 to 1.85) for Europe (I^2=63%, p=0.07), 0.67 (95% CI, 0.39 to 1.14) for North America, and 0.82 (95% CI, 0.41 to 1.66) for Asia. No significant heterogeneity was detected in the latter two regions (Table 6, Fig. 6). Meta-regression analysis did not identify any significant regional interaction (p for interaction=0.92). Regarding dietary retinol intake, the pooled RR was 1.03 (95% CI, 0.73 to 1.48), suggesting no significant association with colorectal adenoma risk (Table 6, Fig. 7). Moderate heterogeneity was present (I^2=52%, p=0.08).

Publication bias was not detected in the analyses of dietary β-carotene intake and vitamin A intake, as confirmed by funnel plot evaluation and Egger's test (p>0.05) (Supplementary Fig. 1).

DISCUSSION

This study examined the association between dietary β-carotene, vitamin A, and retinol intake and the prevalence of colorectal adenoma through FFQ analysis and colonoscopy. We found that higher dietary β-carotene and vitamin A intake were associated with a lower prevalence of colorectal adenoma, while higher retinol intake showed an increasing trend. Our meta-analysis supported a protective effect of dietary β-carotene intake but did not find a significant association for vitamin A. The results for retinol intake varied across studies, suggesting that regional, genetic and study specific factors may influence the outcomes, highlighting the need for further investigation.

Despite evidence from several studies suggesting that β-carotene and vitamin A may reduce the risk of colorectal adenoma,[32-35,37,39] results across studies have been inconsistent.[28,40,42-46] These discrepancies may arise from variations in nutrient intake methods, cooking methods, dietary patterns, and lifestyle factors. For instance, Giovannucci *et*

Table 5. Characteristics of the Included Studies in the Meta-Analysis

Study (year)	Design	Case or control number	Dietary assessment	Exposure details	RR (95% CI, weight)	Adjustments	Area
Enger *et al.* (1996)[32]	Case-control study	488 vs 488	126 FFQ	β-Carotene, Vit A, C, E	β-Carotene 0.8 (0.4–1.3, 11.7%) Vit A 0.90 (0.50–1.50, 12.9%)	Intake of calories, saturated fat, folate, fiber, and alcohol, current smoking status, BMI, race, physical activity, NSAIDs use	USA
Breuer-Katschinski *et al.* (2001)[33]	Case-control study	184 vs 182	Diet history method	Carotenoids, fats	β-Carotene 0.24 (0.11–0.50, 8.5%) Vit A 0.51 (0.23–1.11, 10.3%)	Energy, relative weight, social class	Germany
Steck-Scott *et al.* (2024)[34]	Cohort study (RCT)	419 vs 415	101 FFQ	β-Carotene, Vit A	β-Carotene 0.75 (0.49–1.15, 16.0%) Vit A 0.52 (0.33–0.83, 13.9%)	Age, sex, NSAIDS use, intervention group, sex group interaction	USA
Senesse *et al.* (2005)[35]	Case-control study	362 vs 427	2-hr diet history	β-carotene, Vit	β-Carotene 0.8 (0.5–1.3, 14.5%) Retinol 1.10 (0.70–1.80, 23.7%)	Smoking status, age, sex, BMI, energy, and alcohol intakes	France
Ramadas *et al.* (2010)[36]	Case-control study	59 vs 59	24-hr recall	Fiber, fats	β-Carotene 0.21 (0.07–0.59, 5.1%) Vit A 0.54 (0.17–1.73, 7.0%) Retinol 0.36 (0.13–1.04, 9.1%)	Age, ethnicity, income, alcohol consumption, smoking, energy intake	Malaysia
Jung *et al.* (2013)[37]	Cohort study	29,363	FFQ every 4 yr	Carotenoids, Vit A, C, E	β-Carotene 0.72 (0.64–0.81, 25.7%)	Age, pack years oof smoking before age 30, smoking status, physical activity, family history of colorectal cancer, time-period of endoscopy during follow-up, aspirin use, BMI, energy intake, processed meat consumption, red meat consumption, alcohol, calcium intake, Vit D intake	USA
Jacobs *et al.* (2023)[38]	Cohort study (RCT)	1,874	AFFQ	Selenium, antioxidants	β-Carotene 0.65 (0.48–1.90, 9.7%) Retinol 1.01 (0.74–1.39, 30.9%)	Age, sex, history of colorectal polyps	USA
Olsen *et al.* (1994)[39]	Case-control study	152 vs 312	FFQ	Fiber, fats	Vit A 0.65 (0.40–1.10, 13.4%)	Age, sex, energy intake	Denmark
Nagata *et al.* (2001)[40]	Case-control study	181 vs 12,607 (M) 78 vs 15,574 (F)	169-item FFQ	Protein, fats	Vita A (M) 1.51 (1.04–2.20, 14.9%) Vita A (F) 1.25 (0.73–2.18, 13.0%)	Age, years of smoking, alcohol intake	Japan
Almendingen *et al.* (2001)[27]	Case-control study	87 vs 35	5-day dietary record	Fat, protein, fiber	Vit A 4.30 (0.80–21.60, 4.3%)	BMI, colorectal cancer among first-degree relative, energy, fat, fiber, and smoking status	Norway
Lubin *et al.* (1997)[41]	Case-control study	196 vs 196	Diet questionnaire	Fiber, water	Retinol 0.90 (0.50–1.60, 19.5%)	Energy intake, physical activity	Israel
Current study	Cross-sectional study	266 vs 454	113 FFQ	β-Carotene, Vit A, retinol	β-Carotene 0.43 (0.20–0.91, 8.9%) Vit A 0.34 (0.15–0.76, 10.2%) Retinol 2.16 (1.09–4.29, 16.9%)	Age, sex, total energy intake, center, BMI, smoking, physical activity, educational level, alcohol intake, colon polyp resection history, years since last colonoscopy, hypertension, diabetes, aspirin use, family history of colorectal cancer, calcium intake, and fiber intake	Korea

RR, relative risk; CI, confidence interval; FFQ, food frequency questionnaire; Vit, vitamin; BMI, body mass index; NSAIDs, nonsteroidal anti-inflammatory drugs; RCT, randomized controlled trial; AFFQ, Arizona FFQ; M, male; F, female.

Table 6. Meta-Analyses of the Highest versus Lowest Quartiles Dietary Intake of β-Carotene, Vitamin A, and Retinol and Colorectal Adenoma

Subgroup	β-Carotene intake				Vitamin A intake				Retinol intake			
	No. of studies	Pooled RR (95% CI)	I^2 (%)	p-value	No. of studies	Pooled RR (95% CI)	I^2 (%)	p-value	No. of studies	Pooled RR (95% CI)	I^2 (%)	p-value
All	8	0.60 (0.46–0.78)	56	0.03	8	0.79 (0.53–1.17)	72	<0.01	5	1.03 (0.73–1.48)	52	0.08
Region												
North America	4	0.72 (0.65–0.81)	0	0.97	3	0.67 (0.39–1.14)	56	0.13	1	1.01 (0.74–1.39)	NA	
Europe	2	0.45 (0.14–1.48)	86	<0.01	2	0.82 (0.36–1.85)	63	0.07	1	1.10 (0.70–1.80)	NA	
Asia	2	0.32 (0.18–0.58)	0	0.35	3	0.82 (0.41–1.66)	79	<0.01	3	0.94 (0.40–2.23)	76	0.02

Forest plots of these results are available in Table 6. Egger's test for publication bias: p=0.11 for β-carotene, p=0.60 for vitamin A, and p=0.72 for retinol. p for interaction by region: p=0.06 for β-carotene, p=0.92 for vitamin A, and p=0.98 for retinol.
RR, relative risk; CI, confidence interval; NA, not applicable.

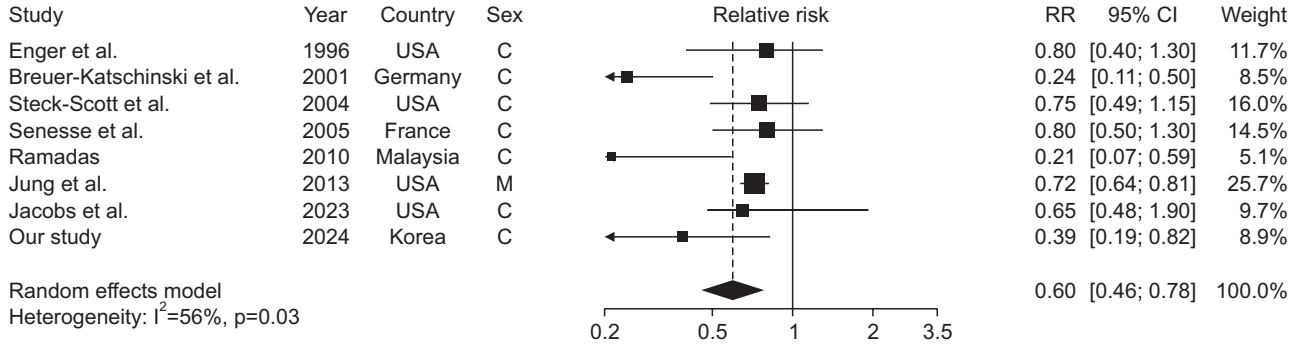

Fig. 3. Forest plot of lowest versus highest quartiles of dietary β-carotene intake in observational studies. The black squares indicate the study-specific RRs; the horizontal lines represent the 95% CIs. The size of each square is proportional to the study weight. The dashed line shows the overall pooled RR, and the diamonds indicate the 95% CIs of the pooled RRs. M, men; C, combined sex; RR, relative risk; CI, confidence interval.

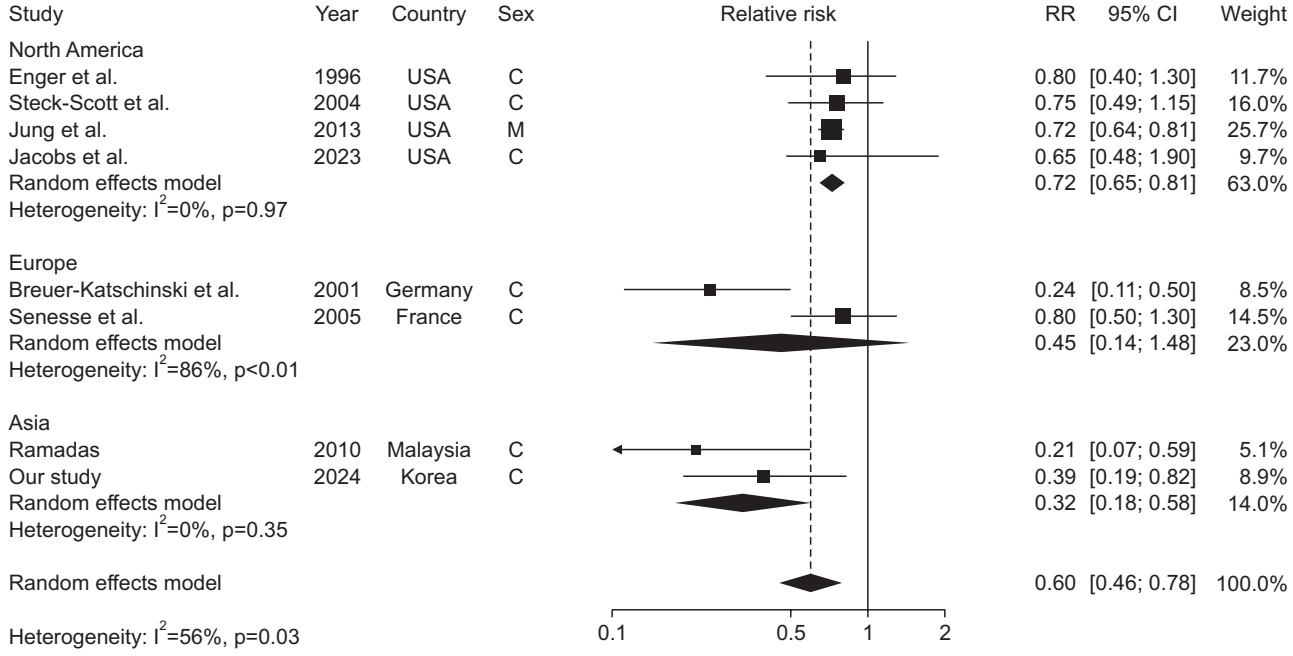

Fig. 4. Forest plot for lowest versus highest quartiles of dietary β-carotene intake in observational studies according to region. The black squares indicate the study-specific RRs; the horizontal lines represent the 95% CIs. The size of each square is proportional to the study weight. The dashed line shows the overall pooled RR, and the diamonds indicate the 95% CIs of the pooled RRs. M, men; C, combined sex; RR, relative risk; CI, confidence interval.

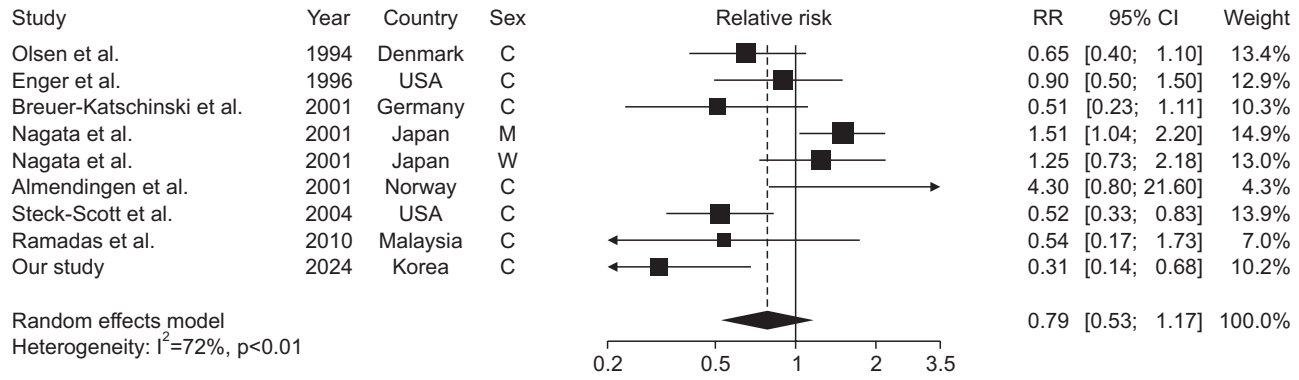

Fig. 5. Forest plot of lowest versus highest quartiles of dietary vitamin A intake in observational studies. The black squares indicate the study-specific RRs; the horizontal lines represent the 95% CIs. The size of each square is proportional to the study weight. The dashed line shows the overall pooled RR, and the diamonds indicate the 95% CIs of the pooled RRs. p for heterogeneity <0.01. M, men; W, women; C, combined sex; RR, relative risk; CI, confidence interval.

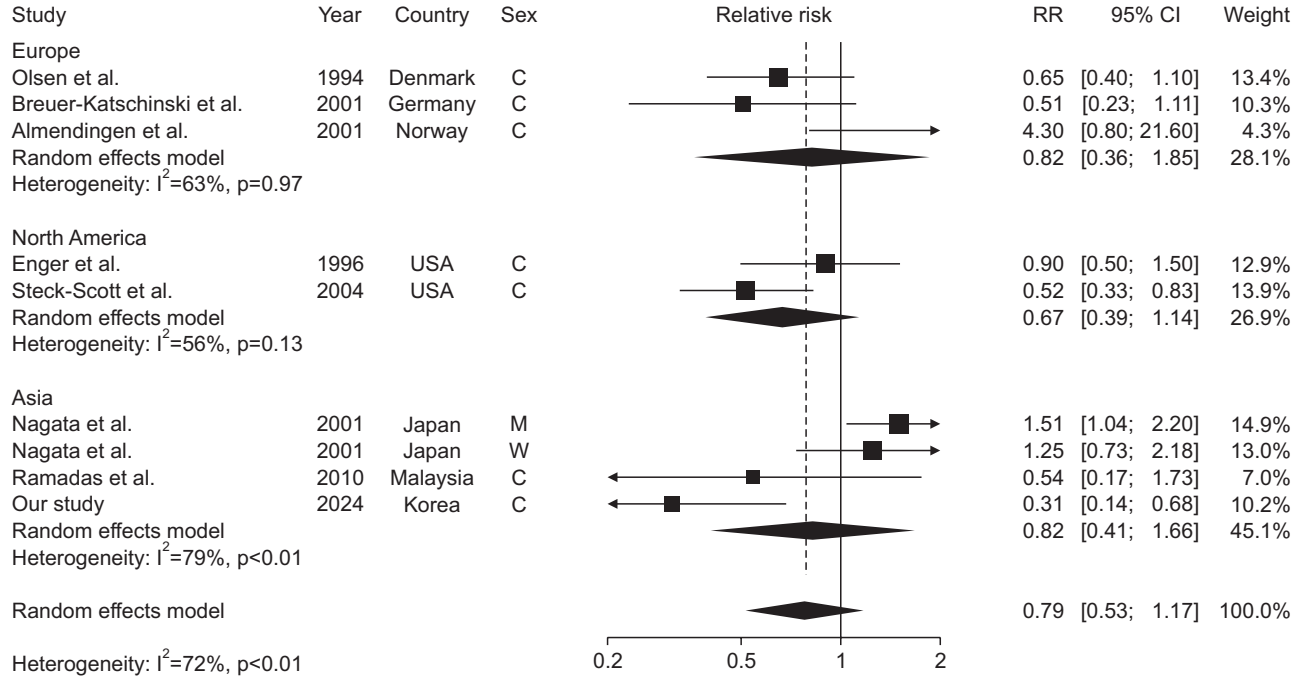

Fig. 6. Forest plot for lowest versus highest quartiles of dietary vitamin A intake in observational studies according to region. The black squares indicate the study-specific RRs; the horizontal lines represent the 95% CIs. The size of each square is proportional to the study weight. The dashed line shows the overall pooled RR, and the diamonds indicate the 95% CIs of the pooled RRs. M, men; W, women; C, combined sex; RR, relative risk; CI, confidence interval.

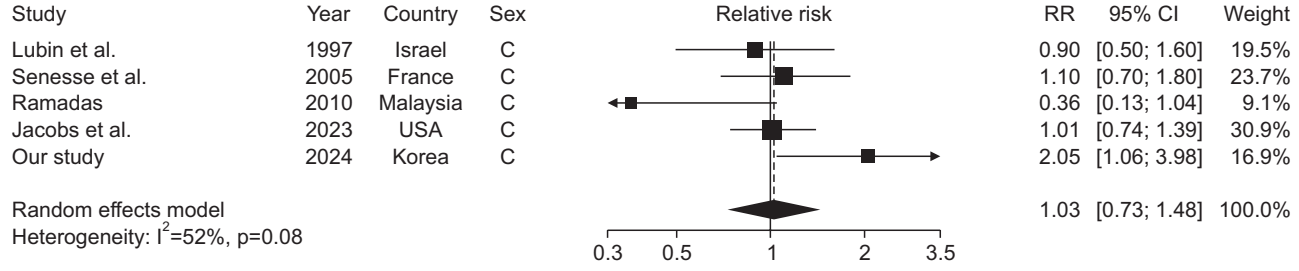

Fig. 7. Forest plot of lowest versus highest quartiles of dietary retinol intake in observational studies. The black squares indicate the study-specific RRs; the horizontal lines represent the 95% CIs. The size of each square is proportional to the study weight. The dashed line shows the overall pooled RR, and the diamonds indicate the 95% CIs of the pooled RRs. p for heterogeneity=0.08. C, combined sex; RR, relative risk; CI, confidence interval.

al.[47] observed an inverse association between β-carotene and colorectal adenoma only in men, whereas Tseng *et al.*[43] found an inverse association for folate, iron, vitamin A, and vitamin C intake in women, but a protective effect of high doses of vitamin E in men. Additionally, the protective effect of β-carotene appears to depend on smoking or alcohol consumption.[35,48,49] These findings suggest that the impact of antioxidants can vary by sex, behavior, physiology, and bioavailability differences.[43] Our meta-analysis further demonstrated that the protective effect of β-carotene was more pronounced in studies conducted in Asia and America compared to Europe (Fig. 4), where considerable heterogeneity was observed.

The inverse association for β-carotene and vitamin A intake was most evident in the distal colon and rectum, while no significant associations were found in the proximal colon (Supplementary Table 4). These subsite-specific differences may reflect distinct biological mechanisms or exposure patterns, although their clinical relevance remains uncertain.

To explore how dietary context influences nutrient effects, we conducted a subgroup analysis stratified by red meat intake. Interestingly, the inverse associations of β-carotene and vitamin A with colorectal adenoma were more pronounced among individuals with higher red meat consumption. Although this may seem counterintuitive, it suggests that certain antioxidants could exert context-specific protective effects in environments characterized by elevated oxidative stress, such as diets rich in red meat.

In contrast, higher retinol intake was associated with increased adenoma prevalence. This finding is inconsistent with some previous studies reporting no significant association with dietary retinol intake.[35,36,38,41] However, considering serum levels of retinol binding protein 4 have been linked to an increased risk of colorectal adenoma, it is plausible that higher retinol intake may indirectly contribute to adenoma development through mechanisms involving retinol binding protein 4.[50] Additionally, it is possible that the observed association reflects broader dietary pattern rather than the direct effect of retinol itself. In our study population, major dietary sources of retinol included liver, egg, yolks, and full-fat dairy products-foods typically associated with animal-based, high-fat diets, while β-carotene is abundant in vegetables such as carrots, spinach, and pumpkin. These contrasting dietary patterns may partly explain the divergent association observed. These findings underscore the complexity of dietary interactions and highlight the importance of considering overall dietary composition, including both protective and risk-enhancing factors, when evaluating nutrient roles in colorectal neoplasia.

Many studies assessing antioxidant efficacy have relied on supplementary intake, which may not reflect the synergic effects present in whole foods.[28,42,44,45,48] Fruits and vegetables contain a broad spectrum of antioxidants that may enhance nutrient absorption and biological activity when consumed together.[8,51] In contrast, supplements consist of isolated, highly purified compounds, which may lack these synergistic interactions. Additionally, substantial variation in supplement doses and nutrient combinations across studies limit conclusions regarding their effectiveness.[52] These limitations reinforce the value of focusing future search on whole-food-based antioxidant intake.

A key strength of our study is its use of colonoscopy-confirmed adenoma diagnosis, unlike many studies relying on self-reported questionnaires. Additionally, we conducted a meta-analysis, integrating our results with case-control and cohort studies to enhance the generalizability of our findings.

Nevertheless, several limitations should be considered. Our study was based on a single ethnic population with a relatively small sample size, although participants were recruited from multiple centers across the country to capture dietary diversity. As a survey-based study, dietary intake data may have misclassification errors. However, FFQs were completed before colonoscopy, minimizing bias, and the FFQs has been validated for the Korean population with proven reliability over year of research.[21] While this cross-sectional design limits causal inference, we adjusted for previous colorectal adenoma history, and plan to conduct long-term follow-up studies to verify causal relationships. Lastly, we did not evaluate interactions with other antioxidants or genetic variants affecting nutrient metabolism.

In summary, our study found that higher dietary β-carotene and vitamin A intake were associated with a lower prevalence of colorectal adenoma, while higher dietary retinol intake was linked to an increased prevalence. These effects varied by dietary composition, particularly in relation to red meat and fat intake. These findings support the potential role of dietary modification-especially increasing β-carotene and vitamin A intake and limiting retinol-rich animal-based foods-in colorectal adenoma prevention. Future prospective studies incorporate genetic analyses and broader antioxidant profiles are warranted to refine dietary guidelines and inform targeted nutritional strategies.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

This work was supported by national grants from the Ministry of Science and ICT, National Research Foundation of Korea (2022R1F1A1066166), Korean Journal of Gastrointestinal Cancer Research Foundation (2024,2021) and Dongguk University Research Fund.

AUTHOR CONTRIBUTIONS

Study concept and design: Y.J.L., J.C. Data acquisition: J.C., S.H.K., M.K.J., D.H.K., H.J.S., K.B.K., S.J.N., Y.J.L. Data analysis and interpretation: J.K., J.C. Drafting of the manuscript: J.C., S.H.K., M.K.J. Critical revision of the manuscript for important intellectual content: J.E.L., Y.J.L., D.H.K., H.J.S., K.B.K., S.J.N., H.J.C. Statistical analysis: J.K., J.E.L. Obtained funding: Y.J.L. Administrative, technical, or material support: H.J.C. Study supervision: Y.J.L. Approval of final manuscript: all authors.

ORCID

Joowon Chung https://orcid.org/0000-0003-1572-8056
Jioh Kang https://orcid.org/0009-0003-9035-9999
Sang Hoon Kim https://orcid.org/0000-0003-3548-1986
Min Kyu Jung https://orcid.org/0000-0001-8749-408X
Dong Hyun Kim https://orcid.org/0000-0001-5778-1264
Hyun Joo Song https://orcid.org/0000-0002-2561-555X
Ki Bae Kim https://orcid.org/0000-0001-6372-432X
Seung-Joo Nam https://orcid.org/0000-0002-0349-0901
Hoon Jai Chun https://orcid.org/0000-0002-5539-361X
Jung Eun Lee https://orcid.org/0000-0003-1141-878X
Yun Jeong Lim https://orcid.org/0000-0002-3279-332X

SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl250104.

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