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CLINICAL AT

Total Vitamin D Intake and Risks of Early-Onset Colorectal Cancer and Precursors

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BACKGROUND & AIMS: Vitamin D has been implicated in colorectal cancer (CRC) pathogenesis, but it remains unknown whether total vitamin D intake is associated with early-onset CRC and precursors diagnosed before age 50. **METHODS:** We prospectively examined the association between total vitamin D intake and risks of early-onset CRC and precursors among women enrolled in the Nurses' Health Study II. Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for early-onset CRC were estimated with Cox proportional hazards model. Multivariable-adjusted odds ratios (ORs) and 95% CIs for early-onset conventional adenoma and serrated polyp were estimated with logistic regression model. **RESULTS:** We documented 111 incident cases of early-onset CRC during 1,250,560 person-years of follow-up (1991 to 2015). Higher total vitamin D intake was significantly associated with a reduced risk of early-onset CRC (HR for ≥450 IU/day vs <300 IU/day, 0.49; 95% CI, 0.26–0.93; *P* for trend = .01). The HR per 400 IU/day increase was 0.46 (95% CI, 0.26–0.83). The inverse association was significant and appeared more evident for dietary sources of vitamin D (HR per 400 IU/day increase, 0.34; 95% CI, 0.15–0.79) than supplemental vitamin D (HR per 400 IU/day increase, 0.77; 95% CI, 0.37–1.62). For CRC precursors, the ORs per 400 IU/day increase were 0.76 (95% CI, 0.65–0.88) for conventional adenoma (n = 1,439) and 0.85 (95% CI, 0.75–0.97) for serrated polyp (n = 1,878). **CONCLUSIONS:** In a cohort of younger women, higher total vitamin D intake was associated with decreased risks of early-onset CRC and precursors.

Keywords: Vitamin D; Colorectal Cancer; Colorectal Adenoma; Cancer Epidemiology.

Despite a decline in the overall incidence of colorectal cancer (CRC) in many countries, including the United States, the incidence of CRC in younger adults has been rising.[1,2] It is projected that by 2030, almost 11% of colon cancers and 23% of rectal cancers will occur among US adults younger than 50 years.[3] Compared with CRC diagnosed after age 50, early-onset CRC (defined as CRC diagnosed before age 50) is typically diagnosed at a more advanced stage, likely owing to delays in diagnosis[4] and potentially more aggressive behavior relating to different clinicopathologic characteristics.[5,6] Because a substantial proportion of early-onset CRC patients do not have a family history of CRC or known hereditary syndrome,[7,8] recent changes in lifestyle factors and dietary patterns are hypothesized to contribute to the increasing incidence of early-onset CRC. Recently, researchers found a significant association between sedentary behaviors,[9] obesity,[10] and increased risk of early-onset CRC in the Nurses' Health Study (NHS) II, suggesting that at least some well known risk factors of traditional CRC may also contribute to early-onset CRC.

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Abbreviations used in this paper: **25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; CRC, colorectal cancer; FFQ, food frequency questionnaire; METS, metabolic equivalent of task score; NHS, Nurses' Health Study; VITAL, Vitamin D and Omega-3 Trial.**

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WHAT YOU NEED TO KNOW:

BACKGROUND AND CONTEXT

Colorectal cancer incidence among adults younger than age 50 (ie, early-onset colorectal cancer) has been increasing. As the etiology of early-onset colorectal cancer remains largely unknown, establishing its risk factors is essential to guide prevention.

NEW FINDINGS

This large prospective cohort study provides evidence that higher total vitamin D intake is associated with reduced risks of early-onset colorectal cancer and precursors.

LIMITATIONS

The findings are based on observational data. Further studies are warranted to assess causality.

IMPACT

If confirmed, ensuring adequate vitamin D intake could be recommended as a strategy for potential colorectal cancer prevention for younger adults.

Vitamin D intake represents a possible factor that may contribute to the recent increase in early-onset CRC incidence. A study reported that vitamin D intake from food sources such as fish, mushrooms, and eggs has decreased since the 1980s.[11] While milk is one of the primary food sources of vitamin D in the United States,[12] milk intake has declined over time.[13] Although vitamin D levels have been extensively studied as a protective factor against CRC,[14–19] it remains unknown whether vitamin D intake is associated with the risk of early-onset CRC.

Because reducing the rising burden of early-onset CRC is a priority in CRC prevention, we sought to determine whether total vitamin D intake is associated with risk of early-onset CRC by analyzing data from the NHS II. We also assessed the relationship for CRC precursors (ie, conventional adenomas and serrated polyps), because most CRC cases arise from adenomas[20] and possibly serrated polyps.[21–23]

Materials and Methods

Study Population

The NHS II is a prospective cohort study of 116,429 female nurses aged 25 to 42 years that began in 1989. Participants are followed every 2 years by self-administered questionnaires on demographics, lifestyle factors, and medical and other health-related information, which are complemented by assessments of dietary intake using validated semiquantitative food frequency questionnaires (FFQs) every 4 years. The study protocol (1999-P-003389) was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, as well as those of participating registries as required.

For the present analysis, we excluded women with inflammatory bowel disease, previous diagnosis of CRC, implausible data for baseline energy intake (<600 or >3500 kcal/d), or missing data for baseline vitamin D intake.

Assessment of Total Vitamin D Intake

Total vitamin D intake was calculated by adding dietary vitamin D intake and supplemental vitamin D intake from vitamin D–specific supplements and multivitamins. Dietary vitamin D intake was derived from the FFQs starting in 1991. The accuracy of the food and nutrient intakes from the FFQ was assessed in several validation studies. The Spearman correlation coefficient between two 7-day dietary records and a 152-item FFQ was 0.60 for energy-adjusted intake of total vitamin D including supplements.[24] In addition, the correlations between intakes estimated from four 1-week diet records and a 61-item FFQ were 0.81 for skim milk and 0.66 for fish,[25] which are the two major food items that contribute to vitamin D intake.

The validity of studying vitamin D intake as a predictor for circulating vitamin D was previously evaluated. The prediction model included age, race, body mass index (BMI), physical activity, alcohol intake, post-menopausal hormone use, ultraviolet-B radiation flux at residence, dietary and supplementary vitamin D intakes, and season of blood draw. In this model predicting plasma 25-hydroxyvitamin D [25(OH)D] levels in the NHS II, ≥400 IU/day compared with <100 IU/day of dietary vitamin D intake was associated with a 2.49 ng/mL increase in predicted plasma 25(OH)D levels and ≥400 IU/day compared with 0 IU/day of supplementary vitamin D intake was associated with a 2.70 ng/mL increase in 25(OH)D levels.[26]

Assessment of Covariates

We calculated BMI based on reported height and weight, with weight updated every 2 years. We assessed total energy, red meat, processed meat, fiber, calcium, folate, and alcohol consumed from the FFQ. We also assessed overall diet quality with the use of the Alternative Healthy Eating Index 2010, where a higher score was associated with reduced risks of cardiovascular disease, diabetes,[27,28] and CRC.[29] Smoking status was updated biennially for calculation of pack-years smoked. Physical activity was self-reported with validated questionnaires every 2 to 4 years.[30] A metabolic equivalent of task score (METS) based on energy expenditure was used to assign to each type of physical activity, and the amount of total physical activity was calculated by multiplying the METS by the mean time spent in each activity. We examined television viewing time as a measure for sedentary behavior because previous studies showed that this specific sedentary behavior was associated with chronic diseases[31] and early-onset CRC.[9] The NHS II participants also regularly provided updated information on regular use of aspirin and other nonsteroidal anti-inflammatory drugs, use of post-menopausal hormone therapy, and family history of CRC among first-degree relatives.

Ascertainment of CRC

Our primary end point was incident early-onset CRC, defined as CRC diagnosed before the age of 50 years. We requested written permission to collect medical records and pathology reports from participants who reported having CRC on biennial questionnaires for confirmation of diagnosis. We also identified unreported lethal CRC cases through family members, the postal system, and the National Death Index. For all deaths due to CRC, we requested consent from the next of kin for acquisition of medical records. Physicians who were

blinded to exposure status reviewed medical records to verify CRC diagnosis and recorded histopathologic findings and anatomic location.

Ascertainment of Colorectal Adenoma Cases

The NHS II participants were asked on each biennial follow-up questionnaire whether they underwent a lower bowel endoscopy (either sigmoidoscopy or colonoscopy), the reasons for endoscopy (whether for routine screening without symptoms or for prior symptoms such as bleeding or abdominal pain), and whether colorectal polyps were diagnosed. Participants who reported a diagnosis of polyp were sent a consent form requesting permission to obtain and review their medical, including endoscopy and pathology, records. Study investigators blinded to exposure status reviewed medical records and recorded anatomic location (proximal colon, distal colon, or rectum), subtype (conventional adenoma or serrated polyp), histology for conventional adenoma (tubular, tubulovillous, or villous adenoma, or adenoma with high-grade dysplasia), number of lesions, and maximum size of the lesion in each patient (large if $\geq$10 mm in diameter). Adenomas were defined as high risk if there was any mention of these features: large size, advanced histology (tubulo-villous/villous adenoma or high-grade dysplasia), or presence of 3 or more. All other adenomas were defined as low-risk adenomas. Serrated polyps included hyperplastic polyps, sessile serrated polyps with or without cytologic dysplasia, and traditional serrated adenomas. When 2 polyps were diagnosed in 1 location, we recorded the most advanced lesion, and whenever conventional adenoma and serrated polyp were detected in 1 location, they were coded as separate end points.

Statistical Analysis

We prospectively evaluated the association between total vitamin D intake and risk of early-onset CRC. Person-time was measured from the return of the baseline questionnaire in 1991 until the date of CRC diagnosis, death from any cause, 50th birthday, or the end of follow-up (June 2015), whichever came first. We used energy-adjusted vitamin D intake that was calculated from the regression-residual method to minimize variation due to energy intake and related measurement error.[32] To better capture long-term behaviors and nutritional status and reduce within-person variations, we used cumulative averages for lifestyle and dietary factors, including total vitamin D intake. We examined the association between total vitamin D intake and risk of early-onset CRC with the use of Cox proportional hazard models to estimate age- and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). The Cox model was stratified by age and year of questionnaire return. Covariates were chosen a priori based on established risk factors for traditional CRC.[33] The primary statistical test was a test for linear trend, which was performed using the median of total vitamin D intake category as a continuous variable. We examined potential nonlinear associations with the use of restricted cubic splines.[34,35]

We also evaluated the association between total vitamin D intake and risk of early-onset conventional adenoma and serrated polyp that occurred at age $<$50 years among those who underwent at least 1 lower endoscopy. We restricted the analysis to those who underwent at least 1 lower endoscopy because polyps are often asymptomatic and only detected during an endoscopy. Once a participant was diagnosed with a polyp or reached age 50, the subsequent follow-up periods were not included in the analysis. We used age- and multivariable-adjusted logistic regression models for longitudinal data to account for repeated observations (multiple endoscopies for a participant) to estimate odds ratios (ORs) and 95% CIs. Using proc genmod in SAS, we fitted a generalized estimating equation.[36] Covariates were chosen a priori based on established risk factors for CRC,[33] because risk factors for CRC and adenoma are similar,[37] and serrated polyp and conventional adenoma share many risk factors.[23]

We performed various stratified and sensitivity analyses. We used the model for predicting plasma 25(OH)D levels developed within our cohort[26] to determine whether predicted 25(OH)D levels are associated with early-onset CRC. We also performed analyses based on anatomic tumor location (colon or rectum) and BMI (BMI $<$25 kg/m^2 or $\geq$25 kg/m^2). Different sources of total vitamin D intake (dietary vitamin D or supplemental vitamin D) were evaluated. In addition, to minimize the possibility that undiagnosed CRC may have contributed to total vitamin D intake, we used lag analyses: We excluded the first 2, 4, and 8 years of follow-up and added 2-, 4-, and 8-year lag periods between vitamin D assessment and each follow-up period to address the possibility of changes in behaviors during the preclinical phase and to evaluate the period that is etiologically relevant. We performed several analyses for adenomas based on histology, anatomic location (proximal colon, distal colon, or rectum), and reason for endoscopy. For adenomas, we also assessed interaction between continuous total vitamin D intake and potential effect modifiers: BMI ($<$25 vs $\geq$25 kg/m^2), total calcium intake ($<$1,100 vs $\geq$1,100 mg/day), physical activity ($<$15 vs $\geq$15 METS-hours/week), and smoking status (ever vs never). We conducted sensitivity analysis for adenomas that occurred at age $<$45 years. Because it could take more than 5 years for an adenoma to develop into cancer, adenomas at age $<$45 may be more relevant for early-onset CRC.

All statistical analyses were 2 sided and P values $<$.05 indicated statistical significance. Analyses were performed with the use of SAS 9.4 (SAS Institute, Cary, NC).

Results

Among the 94,205 women studied, we documented 111 incident cases of early-onset CRC during 1,250,560 person-years of follow-up from 1991 to 2015. The median vitamin D intake was 372 IU/day. Among women younger than age 50, those with higher vitamin D intake tended to have a lower BMI, were less likely to smoke cigarettes, drink alcohol, spend time watching TV, and eat red and processed meat; consumed more dietary fiber, total folate, and total calcium; used more aspirin and multivitamins; and were more likely to be physically active and have a healthy dietary pattern (Table 1).

In the age- and multivariable-adjusted analyses, higher total vitamin D intake was associated with a reduced risk of early-onset CRC (Table 2). In the fully adjusted model, compared with women who consumed $<$300 IU/day of total vitamin D intake, the HRs were 0.51 (95% CI, 0.30–0.86) for those who had 300 to $<$450 IU/day total vitamin D intake and 0.49 (95% CI, 0.26–0.93) for those who had $\geq$450 IU/

Table 1. Baseline Characteristics of Person-Years According to Total Vitamin D Intake Among Women Younger Than 50 Years in the NHS II

Characteristic	Total vitamin D intake, IU/day		
	<300	300-<450	≥450
Mean total vitamin D intake, IU/day	194	370	647
Types of vitamin D intake			
Dietary vitamin D intake, IU/day	175 ± 64	259 ± 93	301 ± 124
Dairy vitamin D intake, IU/day	80 ± 55	143 ± 90	170 ± 115
Person-years	528,107	316,264	406,189
Age, years	41.9 ± 5.2	42.4 ± 5.1	41.9 ± 5.4
White, %	92	94	93
Height, cm	165 ± 7	165 ± 7	165 ± 7
BMI, kg/m^2	25.3 ± 5.6	24.9 ± 5.2	24.7 ± 5.1
Family history of CRC, %	5.6	6.0	5.8
Premenopausal, %	91	91	91
History of diabetes, %	1.9	2.0	2.0
Ever smoker, %	35	32	31
Pack-years among ever smokers	13.4 ± 10.1	11.7 ± 9.2	11.5 ± 9.2
Alcohol intake, g/day	3.6 ± 6.4	3.4 ± 5.7	3.0 ± 5.2
Physical activity, METS-hours/week	20.1 ± 22.9	22.9 ± 24.3	25.5 ± 27.7
TV viewing time, hours/week	9.0 ± 7.9	8.6 ± 7.4	8.3 ± 7.5
Regular aspirin use, %	7.8	9.5	11.4
Regular non-aspirin NSAID use, %	25	25	25
Current use of multivitamins, %	24	49	74
Total energy intake, kcal/day	1798 ± 525	1898 ± 500	1761 ± 486
Red and processed meat intake, servings/week	7.2 ± 4.4	6.6 ± 4.0	5.5 ± 3.6
Dietary fiber intake, g/day	17.8 ± 4.9	18.6 ± 4.9	19.3 ± 5.5
Total folate intake, μg/day	335 ± 119	472 ± 162	731 ± 255
Total calcium intake, mg/day	815 ± 274	1089 ± 300	1324 ± 433
Alternative Healthy Eating Index 2010[a]	42.0 ± 9.3	44.2 ± 9.4	46.2 ± 9.6

NOTE. All values except for age have been directly standardized to age distribution (in 5-year age group) of the participants. For continuous variables, mean ± SD is presented.
BMI, body mass index; CRC, colorectal cancer; METS, metabolic equivalent of task score; NHS, Nurses' Health Study; NSAID, non-steroidal anti-inflammatory drug.
[a]Without alcohol intake.

day total vitamin D intake (P for trend = .01) (Table 2). There was no evidence of a nonlinear association (P for nonlinearity = .50). The HR per 400 IU/day increase was 0.46 (95% CI, 0.26–0.83) (Table 2). We observed similar risk estimates when we restricted our analysis to participants without a family history of CRC (n = 98 cases) and without a lower endoscopy in the past 10 years (n = 104 cases).

We also evaluated differences in sources of vitamin D intake. Both sources of vitamin D intake were inversely associated with early-onset CRC, with a significant and stronger association observed for dietary vitamin D (HR per 400 IU/day increase, 0.34; 95% CI, 0.15–0.79) than supplemental vitamin D (HR per 400 IU/day increase, 0.77; 95% CI, 0.37–1.62) (Table 3). No significant interaction between dietary vitamin D and supplemental vitamin D was found in the NHS II cohort (P for interaction = .81). Among dietary sources, vitamin D from dairy products was the major contributor of this association (HR per 400 IU/day increase, 0.32; 95% CI, 0.12–0.84).

We documented 1,439 newly diagnosed conventional adenomas and 1,878 serrated polyps among 29,186 women

Table 2. Total Vitamin D Intake and Risk of Early-Onset CRC in the NHS II, 1991-2015

		HR (95% CI)		
	Cases/person-years	Age-adjusted model	MV-adjusted model 1[a]	MV-adjusted model 2[b]
Total vitamin D intake, IU/day				
<300	64/528,107	1 [Ref]	1 [Ref]	1 [Ref]
300 to <450	20/316,264	0.52 (0.31–0.86)	0.51 (0.31–0.86)	0.51 (0.30–0.86)
≥450	27/406,189	0.57 (0.36–0.91)	0.56 (0.35–0.88)	0.49 (0.26–0.93)
P for trend[c]		.01	.01	.01
Per 400 IU/day increase		0.61 (0.41–0.91)	0.59 (0.39–0.89)	0.46 (0.26–0.83)

CI, confidence interval; HR, hazard ratio; MV, multivariable; other abbreviations as in Table 1.
[a]Additionally adjusted for nondietary factors: white (yes/no), height (continuous), BMI (continuous), smoking pack-years (continuous), physical activity (continuous), TV viewing time (continuous), alcohol intake (continuous), regular use of aspirin (yes/no), NSAID use (yes/no), family history of CRC (yes/no), and history of lower endoscopy within the previous 10 years (yes/no).
[b]Additionally adjusted for dietary intake (total energy, red/processed meat, dietary fiber, total folate, and Alternative Healthy Eating Index 2010, continuous).
[c]Calculated using the median of each total vitamin D intake category as a continuous variable.

aged <50 years who had at least 1 lower endoscopy from 1991 to 2011. Higher total vitamin D intake was associated with a lower risk of early-onset conventional adenoma and was suggestively associated with serrated polyp (Table 4). Compared with women who consumed <300 IU total vitamin D per day, the multivariable-adjusted OR of any conventional adenoma was 0.71 (95% CI, 0.56–0.89) for those who consumed ≥600 IU/day (*P* for trend = .002), and the multivariable-adjusted OR of any serrated polyp for the same comparison was 0.85 (95% CI, 0.70–1.03; *P* for trend = .11) (Table 4). There was no evidence of a nonlinear association (*P* for nonlinearity = .29 for conventional adenoma and .78 for serrated polyp). The ORs per 400 IU/day increase were 0.76 (95% CI, 0.65–0.88) for conventional adenoma and 0.85 (95% CI, 0.75–0.97) for serrated polyp (Table 4).

Table 3. Sources of Vitamin D Intake and Risk of Early-Onset CRC in the NHS II, 1991-2015

		HR (95% CI)		
	Cases/person-years	Age-adjusted model	MV-adjusted model 1[a]	MV-adjusted model 2[b]
Dietary vitamin D intake, IU/day				
<150	34/271,713	1 [Ref]	1 [Ref]	1 [Ref]
150 to <300	59/662,809	0.75 (0.49–1.14)	0.74 (0.48–1.14)	0.75 (0.48–1.17)
≥300	18/316,038	0.52 (0.29–0.92)	0.50 (0.28–0.90)	0.50 (0.27–0.93)
P for trend[c]		.02	.02	.03
Per 400 IU/day increase		0.36 (0.16–0.80)	0.34 (0.15–0.76)	0.34 (0.15–0.79)
Supplementary vitamin D intake, IU/day				
<150	78/793,230	1 [Ref]	1 [Ref]	1 [Ref]
150-<300	21/245,405	0.87 (0.53–1.42)	0.86 (0.53–1.40)	0.90 (0.51–1.60)
≥300	12/211,925	0.64 (0.35–1.17)	0.63 (0.34–1.17)	0.64 (0.28–1.45)
P for trend[c]		.13	.13	.30
Per 400 IU/day increase		0.74 (0.45–1.20)	0.73 (0.44–1.19)	0.77 (0.37–1.62)

Abbreviations as in Tables 1 and 2.
[a]Additionally adjusted for nondietary factors: white (yes/no), height (continuous), BMI (continuous), smoking pack-years (continuous), physical activity (continuous), TV viewing time (continuous), alcohol intake (continuous), regular use of aspirin (yes/no), NSAID use (yes/no), family history of CRC (yes/no), and history of lower endoscopy within the previous 10 years (yes/no).
[b]Additionally adjusted for dietary intake (total energy, red/processed meat, dietary fiber, total folate, and Alternative Healthy Eating Index 2010, continuous).
[c]Calculated using the median of each total vitamin D intake category as a continuous variable.

Table 4. Total Vitamin D Intake and Risk of Early-Onset Conventional Adenoma and Serrated Polyp in the NHS II, 1991-2011

	No. of cases	OR (95% CI)		
		Age-adjusted model[a]	MV-adjusted model 1[b]	MV-adjusted model 2[c]
Any conventional adenoma				
Total vitamin D intake, IU/day				
<300	589	1 [Ref]	1 [Ref]	1 [Ref]
300 to <450	390	0.85 (0.75–0.97)	0.87 (0.76–0.99)	0.83 (0.71–0.96)
450 to <600	258	0.85 (0.73–0.99)	0.87 (0.75–1.02)	0.80 (0.66–0.97)
≥600	202	0.77 (0.65–0.91)	0.80 (0.68–0.94)	0.71 (0.56–0.89)
P for trend[d]		.001	.01	.002
Per 400 IU/day increase		0.82 (0.74–0.92)	0.85 (0.76–0.94)	0.76 (0.65–0.88)
Any serrated polyp				
Total vitamin D intake, IU/day				
<300	719	1[Ref]	1[Ref]	1[Ref]
300 to <450	518	0.94 (0.84–1.06)	0.96 (0.86–1.08)	0.91 (0.80–1.04)
450 to <600	360	0.98 (0.86–1.12)	1.02 (0.89–1.17)	0.93 (0.79–1.09)
≥600	281	0.88 (0.77–1.02)	0.94 (0.81–1.08)	0.85 (0.70–1.03)
P for trend[d]		.14	.54	.11
Per 400 IU/day increase		0.91 (0.84–1.00)	0.95 (0.87–1.03)	0.85 (0.75–0.97)

OR, odds ratio; other abbreviations as in Tables 1 and 2.
[a]Adjusted for age, time period of endoscopy, time since most recent endoscopy, number of reported endoscopies, and reason for current endoscopy.
[b]Additionally adjusted for nondietary factors: white (yes/no), height (continuous), BMI (in quintiles), alcohol intake (never, 0.1-4.9, 5-14.9, 15+ g/d), smoking (never, 0.1-4.9, 5-19.9, 20-39.9, 40+ pack-years), regular use of aspirin (yes/no), regular use of NSAIDs (yes/no), physical activity (METS in quintiles), TV viewing time (in quintiles), and family history of CRC (yes/no).
[c]Additionally adjusted for dietary intake (total energy intake, red and processed meat intake, dietary fiber intake, total folate intake, and Alternative Healthy Eating Index 2010, in quintiles).
[d]Calculated using the median of each total vitamin D intake category as a continuous variable.

Analysis by tumor anatomic site showed similar inverse associations between total vitamin D intake and risks of early-onset colon and rectal cancer, with significant and stronger association for colon cancer (Supplementary Table 1). Stratified analysis by BMI suggested that the potential beneficial association of vitamin D intake is not different for those with BMI <25 kg/m^2 compared with those with BMI ≥25 kg/m^2 (*P* for interaction = .65) (Supplementary Table 2). Although attenuated, the overall results did not greatly change when we excluded the first 2, 4, and 8 years of follow-up and added 2-, 4-, and 8-year lag periods between vitamin D intake assessment and each follow-up period (Supplementary Table 3).

We observed that the association between continuous vitamin D intake and CRC risk differed based on age at diagnosis (age <50 versus ≥50; *P* for heterogeneity = .04). While vitamin D intake was associated with early-onset CRC risk, we could not detect a statistically significant association with risk of CRC diagnosed at or after age 50 possibly due to limited power (Supplementary Table 4).

The predicted 25(OH)D score analysis showed overall results similar to the main analysis, although it did not reach statistical significance (Supplementary Table 5). For early-onset CRC, the HR per 5-unit increase of predicted score was 0.77 (95% CI, 0.50–1.20) and the HR comparing the highest versus lowest tertile of predicted score was 0.71 (95% CI, 0.37–1.35; *P* for trend = .24) (Supplementary Table 5).

The results remained largely unchanged when we repeated the multivariable analyses additionally adjusting for current multivitamin use (Supplementary Table 6), which is a commonly consumed source of supplemental vitamin D as well as other vitamins and minerals. In addition, because calcium intake may confound the relationship between vitamin D intake and early-onset CRC, we additionally adjusted for total calcium intake in the fully adjusted model (Supplementary Table 7). Adjusting for calcium did not substantially change our results (HR for early-onset CRC per 400 IU/day increase, 0.48; 95% CI, 0.25–0.93) (Supplementary Table 7).

Higher vitamin D intake was associated with decreased risks of both high- and low-risk conventional adenomas (Supplementary Table 8). By anatomic site, we observed stronger inverse associations between total vitamin D intake and risks of early-onset conventional adenomas in the distal colon and rectum compared with those in the proximal colon, although the association was statistically significant only for adenoma in the distal colon (P for trend = .01) (Supplementary Table 9). The inverse association for serrated polyp in the distal colon was statistically significant

(multivariable-adjusted OR comparing those with ≥600 IU/day to <300 IU/day of vitamin D intake, 0.64; 95% CI, 0.48–0.84; P for trend = .001) and stronger than those observed for proximal colon or rectum (Supplementary Table 9). In the analysis stratified by reason for endoscopy, the inverse association was significant only for participants with conventional adenoma who underwent an endoscopy because of screening rather than symptoms, but the difference was not statistically significant (*P* for interaction = .09) (Supplementary Table 10). The overall findings did not largely change for serrated polyps diagnosed before age 45, but there was an attenuation in the association for conventional adenomas diagnosed before age 45 compared with age 50 (Supplementary Table 11). In addition, adjusting for calcium did not substantially change our results for adenomas (Supplementary Table 12). No significant interactions were observed between total vitamin D intake and BMI, total calcium intake, physical activity, and smoking status for conventional adenoma and serrated polyp (all *P* for interaction > .05).

Discussion

In this cohort of young women, higher total vitamin D intake was associated with a reduced risk of early-onset CRC. This risk reduction was mostly driven by dietary vitamin D, particularly from dairy intake. Higher total vitamin D intake was also associated with reduced risks of early-onset CRC precursors.

There is growing evidence supporting an association between vitamin D and risk and mortality of CRC, but there are minimal data on the association between vitamin D and early-onset CRC. Existing literature suggests that higher 25(OH)D levels are associated with a reduced risk of CRC[38] (mostly diagnosed at age ≥50). In a recent large pooling study of 5,706 cases, a 10 ng/mL increment in circulating 25(OH)D was associated with a 19% lower CRC risk in women (95% CI, 0.75–0.87) and a 7% lower risk in men (95% CI, 0.86–1.00) (*P* for heterogeneity by sex = .008).[39] However, in the Vitamin D and Omega-3 Trial (VITAL), 2,000 IU/day of vitamin D_3 supplementation was not associated with a lower risk of CRC (HR, 1.09; 95% CI, 0.73–1.62).[40] A large-scale Mendelian randomization study also did not find an association between genetically determined 25(OH)D levels and CRC (OR, 0.92; 95% CI, 0.76–1.10).[41] The association between vitamin D and CRC could truly be negative as the VITAL and Mendelian randomization studies suggested. However, the power for site-specific cancer analyses in the VITAL trial may have been limited to detect an association, and the follow-up time (median 5.3 years) may have been insufficient for a chemopreventive effect. Also, although Mendelian randomization studies provide evidence for a causal relationship, genetically determined 25(OH)D could only partially explain the variance in vitamin D. In the Mendelian randomization study, 4 single-nucleotide polymorphisms were identified, and each explained about 1% of the 25(OH)D variability.[41] In our study, total vitamin D intake was inversely associated with risk of CRC diagnosed before age 50. There was no significant association among participants at age ≥50, possibly owing to lack of power or differential effects of vitamin D in different age groups. Whether the association is truly stronger in early-onset CRC than in traditional CRC requires further work in a larger sample.

Total vitamin D intake, especially supplemental vitamin D intake, could have secularly increased over time and affected our results. Prevalence of vitamin D supplement use increased from 4.2% in 1986 to 32.3% in 2006 in the NHS I[42] and from 5.1% in 1999 to 19% in 2011 in the National Health and Nutrition Examination Survey.[43] However, we did not see a significant interaction between vitamin D intake and time in our data. In addition, we stratified by age and year of the questionnaire in the Cox model, which controls for confounding by age and secular trends.[44]

Most CRC cases arise from precursor lesions called adenomas through the adenoma-carcinoma sequence.[20] Increasing evidence also suggests that serrated polyps represent another precursor lesion for CRC through a different pathway.[21–23] Studying conventional adenomas and serrated polyps diagnosed at age <50 as precursors could help us understand etiologic contributors to the recent rise in early-onset CRC incidence. In the present study, total vitamin D intake was inversely associated with CRC precursors, with a stronger association for conventional adenoma and suggestive inverse association for serrated polyp. Sensitivity analysis for adenomas at age <45 did not largely change the overall results, although the association became statistically insignificant, possibly owing to lack of power. Consistent results among CRC precursors with larger sample size further support the protective role of vitamin D intake in early-onset CRC.

Previous research suggests that a higher proportion of young CRC patients have tumor in the distal colon or rectum whereas a higher proportion of older CRC patients have tumor in the proximal colon.[45] Our study found that higher total vitamin D intake was more strongly associated with early-onset conventional adenomas in the distal colon and rectum compared with those in the proximal colon. Recent clinical trials demonstrated that the beneficial role of vitamin D in cancer could differ by BMI, with less effect in those with greater BMI.[40,46] However, our findings did not find this trend and should further be explored.

Total oral vitamin D intake does not take into account sunlight exposure, which is the major determinant of 25(OH)D status.[47] Nevertheless, vitamin D intake is an important, measurable contributor to circulating 25(OH)D levels, and the estimates of intake did predict plasma 25(OH)D levels in a sample of the participants.[26] Moreover, in the present study, the association for total vitamin D intake remained even after adjusting for physical activity and TV viewing time, which can potentially reflect sun exposure. Although not statistically significant, the overall results from predicted 25(OH)D score analysis were similar to the main findings. Vitamin D is suggestively protective of early-onset CRC as the predicted 25(OH)D score reflects vitamin D from not only food intake but also sun exposure and variations from other sources.

Notably, our findings were driven by dietary vitamin D rather than supplemental vitamin D. This could be due to chance, but one possible explanation is that dietary vitamin D may capture long-term dietary patterns before the baseline (eg, diet during adolescence), which could be important for early-onset CRC risk, whereas supplemental vitamin D may not reflect supplemental vitamin D intake before the baseline. Another possible explanation is that certain nutrients in multivitamins could offset the beneficial effects of vitamin D. For example, vitamin D was not associated with a lower distal colorectal adenoma risk when retinol intake was high.[48] However, the mechanisms underlying differences between dietary vitamin D intake and supplemental vitamin D intake are not fully understood.

Potential mechanisms that may explain the inverse association between vitamin D intake and risk of CRC include inhibition of proliferation, migration, invasiveness, and angiogenesis of colon carcinoma cells, and regulation of intestinal immune cells.[49] Increasing evidence suggests that the proportion of molecular subtypes differs in the early- and the older-onset CRC. A study that examined consensus molecular subtypes found that subtypes significantly differed by age group ($P = .003$), with subtype 1 being the most common subtype for young patients.[50] In addition, early-onset CRC patients were more likely to present with microsatellite instability and synchronous metastatic disease but less likely to have BRAF V600 mutations.[50] The biological mechanisms pertaining specifically to the association of vitamin D and early-onset CRC require further investigation.

The strengths of our study include prospective design, long-term follow-up of approximately 30 years, and repeated measurements of dietary and lifestyle factors. In addition, ages at enrollment were young (25–42 years), which enabled us to investigate early-onset CRC and adenoma prospectively. We also had relatively wide variation in vitamin D intake and detailed information on many risk factors of CRC and adenoma. We were able to minimize the influence of measurement error by using the cumulative average of total vitamin D intake. We acknowledge several limitations in our study. First, despite the large number of participants in our cohort, we had a limited number of early-onset CRC cases (n = 111), mainly because early-onset CRC remains relatively rare. However, our results were consistent for conventional adenomas (n = 1439) and serrated polyps (n = 1878), which are CRC precursors. Second, the pool of precursors from which early-onset CRC cases arise from includes all precursors before age 50. Because colonoscopy before age 40 is rare, our sample was skewed to those polyps diagnosed mostly from age 40 to 50. Many of these polyps were likely present for years before detection. Third, we could not distinguish whether the results are consistent across all genetic predispositions. However, most of our cases had no family history of CRC and no lower endoscopy within the previous 10 years. We confirmed the protective role of vitamin D intake in sporadic early-onset CRC through the consistent results among participants without a family history of CRC and without a lower endoscopy within the previous 10 years. Fourth, although our analyses controlled for key risk factors, our results could be affected by residual and unmeasured confounding. Fifth, our study population consisted of female nurses (mostly white), which reduces the generalizability of the results.

In conclusion, we found evidence that higher total vitamin D intake is associated with decreased risks of early-onset CRC and precursors. Our results further support that avoiding low vitamin D status is important in younger adults for health and possibly CRC prevention. If confirmed, our findings could potentially lead to recommendations for higher vitamin D intake as an inexpensive low-risk complement to CRC screening as CRC prevention strategy for adults younger than age 50.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of Gastroenterology at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2021.07.002.

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Conflicts of interest
Andrew T. Chan reported receiving consulting fees from Boehringer Ingelheim, Pfizer, and Bayer Pharma. Charles Fuchs has been a consultant and/or a scientific advisor for Eli Lilly, Entrinsic Health, Pfizer, Merck, Sanofi, Roche, Genentech, Merrimack Pharmaceuticals, Dicerna, Bayer, Celgene, Agios, Gilead Sciences, Five Prime Therapeutics, Taiho, and KEW. Kimmie Ng reported the following disclosures for the past 12 months: research funding from Pharmavite, Revolution Medicines, Janssen, and Evergrande Group; advisory boards for Array Biopharma, Seattle Genetics, and BiomX; and consulting for X-Biotix Therapeurics. No other disclosures were reported.

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Data Transparency
Information including the procedures for obtaining and accessing data from the Nurses' Health Studies II is described at www.nurseshealthstudy.org/researchers.

Supplementary Table 1. Total Vitamin D Intake and Risk of Early-Onset CRC According to Anatomic Sites, in the NHS II, 1991-2015

		HR (95% CI)		
	Cases/person-years	Age-adjusted model	MV-adjusted model 1[a]	MV-adjusted model 2[b]
Colon cancer				
Total vitamin D intake, IU/day				
<300	42/528,125	1 [Ref]	1 [Ref]	1 [Ref]
300 to <450	14/316,268	0.57 (0.31–1.05)	0.56 (0.30–1.03)	0.52 (0.27–0.99)
≥450	20/406,195	0.65 (0.38–1.12)	0.63 (0.36–1.09)	0.48 (0.23–1.02)
P for trend[c]		.09	.07	.03
Per 400 IU/day increase		0.65 (0.40–1.05)	0.63 (0.39–1.03)	0.40 (0.21–0.78)
Rectal cancer				
Total vitamin D intake, IU/day				
<300	22/528,141	1 [Ref]	1 [Ref]	1 [Ref]
300 to <450	6/316,276	0.43 (0.17–1.07)	0.44 (0.18–1.09)	0.50 (0.19–1.33)
≥450	7/406,202	0.43 (0.18–1.01)	0.43 (0.18–1.03)	0.53 (0.15–1.84)
P for trend[c]		.04	.04	.24
Per 400 IU/day increase		0.52 (0.25–1.09)	0.53 (0.25–1.11)	0.72 (0.25–2.06)

BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; MV, multivariable; NHS, Nurses' Health Study; NSAID, non-steroidal antiinflammatory drug.

[a]Additionally adjusted for nondietary factors: white (yes/no), height (continuous), BMI (continuous), smoking pack-years (continuous), physical activity (continuous), TV viewing time (continuous), alcohol intake (continuous), regular use of aspirin (yes/no), NSAID use (yes/no), family history of CRC (yes/no), and history of lower endoscopy within the previous 10 years (yes/no).

[b]Additionally adjusted for dietary intake: total energy, red/processed meat, dietary fiber, total folate, and Alternative Healthy Eating Index 2010, continuous.

[c]Calculated using the median of each total vitamin D intake category as a continuous variable.

Supplementary Table 2. Total Vitamin D Intake and Risk of Early-Onset CRC According to BMI, in the NHS II, 1991-2015

		HR (95% CI)			
	Cases/person-years	Age-adjusted model	MV-adjusted model 1[a]	MV-adjusted model 2[b]	*P* for interaction[c]
BMI <25 kg/m^2					
Total vitamin D intake, IU/day					
<300	29/323,951	1 [Ref]	1 [Ref]	1 [Ref]	.65
300 to <450	13/199,204	0.73 (0.37–1.41)	0.70 (0.36–1.37)	0.68 (0.34–1.36)	
≥450	15/266,843	0.63 (0.34–1.19)	0.61 (0.32–1.15)	0.54 (0.23–1.28)	
P for trend[d]		.15	.12	.14	
Per 400 IU/day increase		0.66 (0.39–1.13)	0.63 (0.37–1.08)	0.49 (0.23–1.06)	
BMI ≥25 kg/m^2					
Total vitamin D intake, IU/day					
<300	35/204,157	1 [Ref]	1 [Ref]	1 [Ref]	
300 to <450	7/117,060	0.34 (0.15–0.78)	0.33 (0.14–0.76)	0.34 (0.14–0.80)	
≥450	12/139,346	0.53 (0.27–1.03)	0.50 (0.26–0.99)	0.45 (0.17–1.22)	
P for trend[d]		.03	.02	.05	
Per 400 IU/day increase		0.54 (0.29–1.02)	0.52 (0.27–0.97)	0.43 (0.17–1.11)	

Abbreviations as in Supplementary Table 1.

[a]Additionally adjusted for nondietary factors: white (yes/no), height (continuous), smoking pack-years (continuous), physical activity (continuous), TV viewing time (continuous), alcohol intake (continuous), regular use of aspirin (yes/no), NSAID use (yes/no), family history of CRC (yes/no), and history of lower endoscopy within the previous 10 years (yes/no).

[b]Additionally adjusted for dietary intake: total energy, red/processed meat, dietary fiber, total folate, and Alternative Healthy Eating Index 2010, continuous.

[c]*P* for interaction between BMI (<25 vs ≥25 kg/m^2) and continuous total vitamin D intake.

[d]Calculated using the median of each total vitamin D intake category as a continuous variable.

Supplementary Table 3. Total Vitamin D Intake and Risk of Early-Onset CRC, With Lag Periods, in the NHS II, 1991-2015

	Total vitamin D intake, IU/day, with lag				
	<300	300 to <450	≥450	*P* for trend[a]	Per 400 IU/day increase
2-year lag					
No. of cases	53	18	25		
No. of person-years	452,442	263,875	342,877		
Age-adjusted HR (95% CI)	1 [Ref]	0.56 (0.33–0.97)	0.64 (0.39–1.03)	.06	0.73 (0.48–1.10)
MV-adjusted HR (95% CI)[b]	1 [Ref]	0.50 (0.22–1.12)	0.53 (0.24–1.16)	.12	0.86 (0.43–1.71)
4-year lag					
No. of cases	41	12	21		
No. of person-years	305,650	182,783	237,906		
Age-adjusted HR (95% CI)	1 [Ref]	0.51 (0.26–0.97)	0.67 (0.39–1.16)	.17	0.77 (0.49–1.21)
MV-adjusted HR (95% CI)[b]	1 [Ref]	0.48 (0.20–1.14)	0.46 (0.20–1.06)	.08	0.64 (0.30–1.35)
8-year lag					
No. of cases	20	11	12		
No. of person-years	171,138	98,924	138,738		
Age-adjusted HR (95% CI)	1 [Ref]	0.94 (0.44–1.98)	0.71 (0.33–1.50)	.36	1.01 (0.59–1.73)
MV-adjusted HR (95% CI)[b]	1 [Ref]	0.99 (0.46–2.13)	0.69 (0.31–1.50)	.35	0.98 (0.57–1.68)

Abbreviations as in Supplementary Table 1.
[a]Calculated using the median of each total vitamin D intake category as a continuous variable.
[b]Additionally adjusted for nondietary factors [white (yes/no), height (continuous), BMI (continuous), smoking pack-years (continuous), physical activity (continuous), TV viewing time (continuous), alcohol intake (continuous), regular use of aspirin (yes/no), NSAID use (yes/no), family history of CRC (yes/no), and history of lower endoscopy within the previous 10 years (yes/no)] and dietary intake [total energy, red/processed meat, dietary fiber, total folate, and Alternative Healthy Eating Index 2010, continuous].

Supplementary Table 4. Total Vitamin D Intake and Risk of CRC Diagnosed at Age 50 and Above, NHS II 1991-2015

		HR (95% CI)			
Cases / Person-years		Age-adjusted model	MV-adjusted model 1[a]	MV-adjusted model 2[b]	*P* for heterogeneity[c]
Total vitamin D intake (IU/day)					0.04
<300	72 / 286,771	1 [Ref]	1 [Ref]	1 [Ref]	
300-<450	63 / 245,251	1.02 (0.73–1.43)	1.07 (0.76–1.50)	1.06 (0.74–1.51)	
≥450	103 / 420,102	0.96 (0.71–1.31)	1.05 (0.77–1.44)	1.04 (0.69–1.56)	
P for trend[d]		0.72	0.84	0.95	
Per 400 IU/day increase		0.92 (0.74–1.16)	0.99 (0.78–1.24)	0.93 (0.66–1.30)	

Abbreviations as in Supplementary Table 1.
[a]Additionally adjusted for nondietary factors: White (yes/no), height (continuous), BMI (continuous), smoking pack-years (continuous), physical activity (continuous), TV viewing time (continuous), alcohol intake (continuous), regular use of aspirin (yes/no), NSAID use (yes/no), post-menopausal hormone use (pre- menopause, never, and past/current use of menopausal hormones), family history of CRC (yes/no), and history of lower endoscopy within the previous 10 years (yes/no).
[b]Additionally adjusted for dietary intake (total energy, red/processed meat, dietary fiber, total folate, and Alternative Healthy Eating Index 2010, continuous).
[c]*P* for heterogeneity between CRC diagnosed at age <50 and ≥50. Calculated using the likelihood ratio test where models were fitted with a data duplication method.
[d]Calculated using the median of each total vitamin D intake category as a continuous variable.

Supplementary Table 5. Predicted 25(OH)D Score and Risk of CRC, NHS II 1991-2015

	Median predicted score	Cases / Person-years	HR (95% CI)		
			Age-adjusted model	MV-adjusted model 1[a]	MV-adjusted model 2[b]
Early-onset (Age <50)					
Predicted 25(OH)D score (ng/mL)					
Q1	27.3	50 / 400,736	1 [Ref]	1 [Ref]	1 [Ref]
Q2	31.2	30 / 419,174	0.60 (0.38–0.95)	0.61 (0.36–1.03)	0.63 (0.37–1.08)
Q3	34.2	31 / 427,069	0.66 (0.42–1.03)	0.62 (0.34–1.15)	0.71 (0.37–1.35)
P for trend[c]			0.04	0.11	0.24
Per 5-unit increase			0.78 (0.60–1.00)	0.72 (0.48–1.08)	0.77 (0.50–1.20)
CRC at age ≥50					
Predicted 25(OH)D score (ng/mL)					
Q1	27.3	88 / 330,433	1 [Ref]	1 [Ref]	1 [Ref]
Q2	31.2	78 / 313,295	0.90 (0.66–1.23)	0.95 (0.65–1.38)	0.94 (0.64–1.37)
Q3	34.2	71 / 305,947	0.88 (0.64–1.20)	0.98 (0.63–1.55)	0.96 (0.59–1.54)
P for trend[c]			0.39	0.92	0.84
Per 5-unit increase			0.90 (0.75–1.07)	0.89 (0.66–1.21)	0.85 (0.61–1.19)

25(OH)D, 25-hydroxyvitamin D; other abbreviations as in Supplementary Table 1.

[a]Additionally adjusted for nondietary factors: White (yes/no), height (continuous), BMI (continuous), smoking pack-years (continuous), physical activity (continuous), TV viewing time (continuous), alcohol intake (continuous), regular use of aspirin (yes/no), NSAID use (yes/no), family history of CRC (yes/no), and history of lower endoscopy within the previous 10 years (yes/no). Analyses among participants aged ≥50 were also adjusted for post-menopausal hormone use (pre-menopause, never, and past/current use of menopausal hormones).

[b]Additionally adjusted for dietary intake (total energy, red/processed meat, dietary fiber, total folate, and Alternative Healthy Eating Index 2010, continuous)

[c]Calculated using the median of each predicted 25(OH)D score quartile as a continuous variable.

Supplementary Table 6. Total Vitamin D Intake and Risk of Early-Onset CRC, Additionally Adjusted for Current Multivitamin Usage, in the NHS II, 1991-2015

	Total vitamin D intake, IU/day				
	<300	300 to <450	≥450	*P* for trend[a]	Per 400 IU/day increase
No. of cases	64	20	27		
No. of person-years	528,107	316,264	406,189		
Age-adjusted HR (95% CI)	1 [Ref]	0.52 (0.31–0.86)	0.57 (0.36–0.91)	.01	0.61 (0.41–0.91)
MV-adjusted HR (95% CI)[b]	1 [Ref]	0.51 (0.30–0.86)	0.49 (0.26–0.93)	.01	0.46 (0.26–0.83)
MV-adjusted HR (95% CI), additionally adjusted for multivitamin	1 [Ref]	0.52 (0.30–0.89)	0.52 (0.27–1.00)	.02	0.48 (0.27–0.88)

Abbreviations as in Supplementary Table 1.
[a]Calculated using the median of each total vitamin D intake category as a continuous variable.
[b]Additionally adjusted for nondietary factors [white (yes/no), height (continuous), BMI (continuous), smoking pack-years (continuous), physical activity (continuous), TV viewing time (continuous), alcohol intake (continuous), regular use of aspirin (yes/no), NSAID use (yes/no), family history of CRC (yes/no), history of lower endoscopy within the previous 10 years (yes/no)] and dietary intake [total energy, red/processed meat, dietary fiber, total folate, and Alternative Healthy Eating Index 2010, continuous].

Supplementary Table 7. Total Vitamin D Intake and Risk of Early-Onset CRC, Additionally Adjusted for Total Calcium Intake, in the NHS II, 1991-2015

		HR (95% CI)			
	Cases/person-years	Age-adjusted model	MV-adjusted model 1[a]	MV-adjusted model 2[b]	Calcium-adjusted model[c]
Total vitamin D intake, IU/day					
<300	64/528,107	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]
300 to <450	20/316,264	0.52 (0.31–0.86)	0.52 (0.31–0.86)	0.51 (0.30–0.86)	0.53 (0.30–0.91)
≥450	27/406,189	0.57 (0.36–0.91)	0.56 (0.35–0.88)	0.49 (0.26–0.93)	0.52 (0.26–1.03)
P for trend[d]		.01	.01	.01	.03
Per 400 IU/day increase		0.61 (0.41–0.91)	0.59 (0.39–0.89)	0.46 (0.26–0.83)	0.48 (0.25–0.93)

Abbreviations as in Supplementary Table 1.
[a]Additionally adjusted for nondietary factors: white (yes/no), height (continuous), BMI (continuous), smoking pack-years (continuous), physical activity (continuous), TV viewing time (continuous), alcohol intake (continuous), regular use of aspirin (yes/no), NSAID use (yes/no), family history of CRC (yes/no), and history of lower endoscopy within the previous 10 years (yes/no).
[b]Additionally adjusted for dietary intake: total energy, red/processed meat, dietary fiber, total folate, and Alternative Healthy Eating Index 2010, continuous.
[c]Additionally adjusted for total calcium intake (continuous).
[d]Calculated using the median of each total vitamin D intake category as a continuous variable.

Supplementary Table 8. Total Vitamin D Intake and Risk of Early-Onset Conventional Adenoma According to Risk Classification, in the NHS II, 1991-2011

	Total vitamin D intake (IU/day)					
Risk classification	<300	300 to <450	450 to <600	≥600	*P* for trend[a]	Per 400 IU/day increase
High risk[b]						
No. of cases	199	118	95	55		
MV-adjusted OR (95% CI)[c]	1 [Ref]	0.79 (0.62–1.01)	0.93 (0.68–1.27)	0.60 (0.40–0.90)	.03	0.72 (0.55–0.94)
Low risk						
No. of cases	370	252	147	139		
MV-adjusted OR (95% CI)[c]	1 [Ref]	0.81 (0.67–0.97)	0.68 (0.53–0.87)	0.72 (0.54–0.95)	.01	0.75 (0.62–0.91)

OR, odds ratio; other abbreviations as in Supplementary Table 1.
[a]Calculated using the median intake of each total vitamin D intake category as a continuous variable.
[b]Defined as high risk if large size (≥10 mm in diameter), advanced histology (tubulo-villous/villous adenoma or high-grade dysplasia), or ≥3 adenomas.
[c]Adjusted for the same set of covariates as in the last multivariable model in Table 4.

Supplementary Table 9. Total Vitamin D Intake and Risk of Early-Onset Conventional Adenoma and Serrated Polyp According to Anatomic Sites, in the NHS II, 1991-2011

	Total vitamin D intake, IU/day					
	<300	300 to <450	450 to <600	≥600	*P* for trend[a]	Per 400 IU/day increase
Any conventional adenoma						
Proximal colon						
No. of cases	230	174	119	95		
MV-adjusted OR (95% CI)[b]	1 [Ref]	0.96 (0.77–1.20)	0.99 (0.75–1.31)	0.94 (0.67–1.30)	.68	0.92 (0.75–1.14)
Distal colon						
No. of cases	308	185	130	98		
MV-adjusted OR (95% CI)[b]	1 [Ref]	0.74 (0.60–0.91)	0.76 (0.59–0.99)	0.64 (0.47–0.89)	.01	0.71 (0.57–0.88)
Rectum						
No. of cases	98	70	39	35		
MV-adjusted OR (95% CI)[b]	1 [Ref]	0.92 (0.65–1.30)	0.71 (0.44–1.16)	0.63 (0.36–1.10)	.11	0.61 (0.41–0.92)
Any serrated polyp						
Proximal colon						
No. of cases	282	203	149	108		
MV-adjusted OR (95% CI)[b]	1 [Ref]	0.91 (0.74–1.12)	1.03 (0.80–1.32)	0.96 (0.70–1.32)	.91	0.96 (0.79–1.16)
Distal colon						
No. of cases	383	239	158	129		
MV-adjusted OR (95% CI)[b]	1 [Ref]	0.76 (0.63–0.92)	0.71 (0.56–0.90)	0.64 (0.48–0.84)	.001	0.70 (0.58–0.85)
Rectum						
No. of cases	249	193	128	100		
MV-adjusted OR (95% CI)[b]	1 [Ref]	1.00 (0.81–1.24)	0.95 (0.73–1.25)	0.85 (0.62–1.17)	.32	0.81 (0.65–1.00)

Abbreviations as in Supplementary Tables 1 and 8.
[a]Calculated using the median intake of each total vitamin D intake category as a continuous variable.
[b]Adjusted for the same set of covariates as in the last multivariable model in Table 4.

Supplementary Table 10. Total Vitamin D Intake and Risk of Early-Onset Conventional Adenoma and Serrated Polyp by Reason for Endoscopy, in the NHS II, 1991-2011

	Total vitamin D intake, IU/day						
	<300	300 to <450	450 to <600	≥600	*P* for trend[a]	*P* for interaction	Per 400 IU/day increase
Any conventional adenoma							
Screening as reason for current endoscopy							
No. of cases	309	218	138	104		.09	
Age-adjusted OR (95% CI)[b]	1 [Ref]	0.83 (0.70–1.00)	0.75 (0.61–0.92)	0.66 (0.53–0.83)	<.001		0.75 (0.64–0.87)
MV-adjusted OR (95% CI)[c]	1 [Ref]	0.79 (0.65–0.96)	0.69 (0.54–0.90)	0.58 (0.43–0.79)	<.001		0.67 (0.54–0.83)
Symptoms as reason for current endoscopy							
No. of cases	264	152	101	93			
Age-adjusted OR (95% CI)[b]	1 [Ref]	0.83 (0.68–1.02)	0.90 (0.71–1.14)	0.91 (0.71–1.16)	.40		0.89 (0.76–1.04)
MV-adjusted OR (95% CI)[c]	1 [Ref]	0.82 (0.65–1.03)	0.85 (0.64–1.15)	0.88 (0.62–1.26)	.45		0.83 (0.66–1.04)
Any serrated polyp							
Screening as reason for current endoscopy							
No. of cases	374	283	199	169		.87	
Age-adjusted OR (95% CI)[b]	1 [Ref]	0.91 (0.78–1.07)	0.91 (0.77–1.09)	0.90 (0.75–1.09)	.23		0.91 (0.81–1.03)
MV-adjusted OR (95% CI)[c]	1 [Ref]	0.87 (0.73–1.05)	0.85 (0.68–1.07)	0.82 (0.64–1.06)	.11		0.83 (0.70–0.98)
Symptoms as reason for current endoscopy							
No. of cases	314	213	143	101			
Age-adjusted OR (95% CI)[b]	1 [Ref]	0.98 (0.82–1.18)	1.07 (0.87–1.32)	0.83 (0.66–1.04)	.29		0.90 (0.79–1.03)
MV-adjusted OR (95% CI)[c]	1 [Ref]	0.96 (0.79–1.18)	1.04 (0.81–1.35)	0.86 (0.63–1.19)	.56		0.88 (0.72–1.08)

Abbreviations as in Supplementary Tables 1 and 8.
[a]Calculated using the median intake of each total vitamin D intake category as a continuous variable.
[b]Adjusted for age, time period of endoscopy, time since most recent endoscopy, and number of reported endoscopies.
[c]Additionally adjusted for nondietary factors [white (yes/no), height (continuous), BMI (in quintiles), alcohol intake (never, 0.1–4.9, 5–14.9, 15+ g/d), smoking (never, 0.1–4.9, 5–19.9, 20–39.9, 40+ pack-years), regular use of aspirin (yes/no), regular use of NSAIDs (yes/no), physical activity (METS in quintiles), TV viewing time (in quintiles), family history of CRC (yes/no)], and dietary intake [total energy intake, red and processed meat intake, dietary fiber intake, total folate intake, and Alternative Healthy Eating Index 2010, in quintiles].

Supplementary Table 11. Total Vitamin D Intake and Risk of Early-Onset Conventional Adenoma and Serrated Polyp for Participants Aged <45 Years, in the NHS II, 1991-2011

	No. of cases	OR (95% CI)		
		Age-adjusted model[a]	MV-adjusted model 1[b]	MV-adjusted model 2[c]
Any conventional adenoma				
Total vitamin D intake, IU/day				
<300	188	1 [Ref]	1 [Ref]	1 [Ref]
300 to <450	123	0.98 (0.78-1.24)	0.98 (0.78-1.25)	0.92 (0.71-1.20)
450 to <600	73	0.94 (0.71-1.24)	0.96 (0.73-1.27)	0.88 (0.62-1.25)
≥600	59	0.82 (0.61-1.10)	0.84 (0.62-1.13)	0.80 (0.52-1.22)
P for trend[d]		.19	.27	.29
Per 400 IU/day increase		0.87 (0.73–1.03)	0.88 (0.74–1.05)	0.82 (0.63–1.07)
Any serrated polyp				
Total vitamin D intake, IU/day				
<300	261	1 [Ref]	1 [Ref]	1 [Ref]
300 to <450	163	0.92 (0.75-1.12)	0.94 (0.76-1.15)	0.83 (0.66-1.04)
450 to <600	128	1.15 (0.93-1.44)	1.19 (0.95-1.49)	0.95 (0.71-1.27)
≥600	86	0.85 (0.66-1.09)	0.89 (0.69-1.14)	0.71 (0.50-1.01)
P for trend[d]		.57	.85	.10
Per 400 IU/day increase		0.94 (0.81–1.08)	0.96 (0.83–1.11)	0.79 (0.63–1.00)

Abbreviations as in Supplementary Tables 1 and 8.
[a]Adjusted for age, time period of endoscopy, time since most recent endoscopy, number of reported endoscopies, and reason for current endoscopy.
[b]Additionally adjusted for nondietary factors: white (yes/no), height (continuous), BMI (in quintiles), alcohol intake (never, 0.1–4.9, 5–14.9, 15+ g/d), smoking (never, 0.1–4.9, 5–19.9, 20–39.9, 40+ pack-years), regular use of aspirin (yes/no), regular use of NSAIDs (yes/no), physical activity (METS in quintiles), TV viewing time (in quintiles), and family history of CRC (yes/no).
[c]Additionally adjusted for dietary intake: total energy intake, red and processed meat intake, dietary fiber intake, total folate intake, and Alternative Healthy Eating Index 2010, in quintiles.
[d]Calculated using the median of each total vitamin D intake category as a continuous variable.

Supplementary Table 12. Total Vitamin D Intake and Risk of Early-Onset Conventional Adenoma and Serrated Polyp, Additionally Adjusted for Total Calcium Intake, in the NHS II, 1991-2011

	No. of cases	OR (95% CI)			
		Age-adjusted model[a]	MV-adjusted model 1[b]	MV-adjusted model 2[c]	Calcium-adjusted model[d]
Any conventional adenoma					
Total vitamin D intake, IU/day					
<300	589	1 [Ref]	1 [Ref]	1 [Ref]	1 [Ref]
300 to <450	390	0.85 (0.75–0.97)	0.87 (0.76–0.99)	0.83 (0.71–0.96)	0.82 (0.70–0.96)
450 to <600	258	0.85 (0.73–0.99)	0.87 (0.75–1.02)	0.80 (0.66–0.97)	0.81 (0.66–0.99)
≥600	202	0.77 (0.65–0.91)	0.80 (0.68–0.94)	0.71 (0.56–0.89)	0.73 (0.57–0.93)
P for trend[e]		.001	.01	.002	.01
Per 400 IU/day increase		0.82 (0.74–0.92)	0.85 (0.76–0.94)	0.76 (0.65–0.88)	0.76 (0.64–0.90)
Any serrated polyp					
Total vitamin D intake, IU/day					
<300	719	1 [Ref]	1 [Ref]	1 [Ref]	
300 to <450	518	0.94 (0.84–1.06)	0.96 (0.86–1.08)	0.91 (0.80–1.04)	0.87 (0.76–1.00)
450 to <600	360	0.98 (0.86–1.12)	1.02 (0.89–1.17)	0.93 (0.79–1.09)	0.89 (0.74–1.06)
≥600	281	0.88 (0.77–1.02)	0.94 (0.81–1.08)	0.85 (0.70–1.03)	0.83 (0.67–1.02)
P for trend[e]		.14	.54	.11	.09
Per 400 IU/day increase		0.91 (0.84–1.00)	0.95 (0.87–1.03)	0.85 (0.75–0.97)	0.82 (0.72–0.95)

Abbreviations as in Supplementary Tables 1 and 8.
[a]Adjusted for age, time period of endoscopy, time since most recent endoscopy, number of reported endoscopies, and reason for current endoscopy.
[b]Additionally adjusted for nondietary factors: white (yes/no), height (continuous), BMI (in quintiles), alcohol intake (never, 0.1–4.9, 5–14.9, 15+ g/d), smoking (never, 0.1–4.9, 5–19.9, 20–39.9, 40+ pack-years), regular use of aspirin (yes/no), regular use of NSAIDs (yes/no), physical activity (METS in quintiles), TV viewing time (in quintiles), and family history of CRC (yes/no).
[c]Additionally adjusted for dietary intake: total energy intake, red and processed meat intake, dietary fiber intake, total folate intake, and Alternative Healthy Eating Index 2010, in quintiles.
[d]Additionally adjusted for total calcium intake (in quintiles).
[e]Calculated using the median of each total vitamin D intake category as a continuous variable.