Supplementary Material

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Supplementary Methods

Additional detail on calibration of previously measured 25(OH)D and season standardization:

For each study that had previously measured 25(OH)D concentrations, individual 25(OH)D levels were first calibrated to the same assay used for the newly measured studies (direct, competitive chemiluminescence immunoassay at Heartland Assays, LLC) according to $Y_{calibrated} = \hat{a} + \hat{b}Y_{original}$, where the estimates $\hat{a}$ and $\hat{b}$ were obtained by regressing Heartland Assays 25(OH)D on the original 25(OH)D values for 29 calibration samples[1]. In each study, approximately three control participants had been selected within each decile of the study-specific 25(OH)D distribution to serve as calibration samples and were re-assayed at Heartland Assays. Variances for the continuous 25(OH)D analyses were increased to account for laboratory error in the calibration process; variances for the categorical analyses did not need to be similarly adjusted[1]. In studies where the 25(OH)D concentrations were newly measured for this project by Heartland Assays, no calibration was required.

For most studies, seasonal variation in 25(OH)D concentrations followed a sinusoidal distribution, with lowest values in the winter and highest in the summer. To remove variation in circulating 25(OH)D due to season of blood collection, individual residuals from the study-specific sine-cosine function,

$$\{\gamma_0 + \gamma_1 \sin(2\pi t/52) + \gamma_2 \cos(2\pi t/52) + \gamma_3 \sin(4\pi t/52) + \gamma_4 \cos(4\pi t/52), \text{ fitted to controls}\}$$

were added to $\hat{\gamma}_0$. Here $t = 1, 2, \ldots 52$ indexes the week of blood draw. Because the sinusoidal components integrate to zero over the year, $\hat{\gamma}_0$ represents the study-specific average 25(OH)D over the entire year.

Quality control outlier criteria:

The following were used to evaluate quality control: 1) the Westgard multi-rule quality control criteria[2] and 2) examination of study-specific within-batch, between-batch, and overall coefficients of variation (CVs) and intraclass correlation coefficients for the three National Institute of Standards and Technology (NIST) standards and the study-specific quality control samples. For the batches that violated the Westgard rules or had study-specific overall CVs or batch-specific CVs larger than 10% (15% for NIST standard 1), the circulating 25(OH)D distribution of the control samples in that batch was compared with the 25(OH)D distributions for other batches from the same study. In addition, visual examination using Q –Q plots was used to identify potential outliers. No batches or outliers were removed on the basis of the above criteria.

Matching criteria for each cohort:

In addition to all cohorts matching case and control participants on age, date of blood draw, and sex (if applicable), the following cohorts included additional matching factors as listed:

ATBC1: Study clinic
BGS: Ethnicity, year of entry into cohort, number of days between blood draw and processing
CARET: Race
CLUE II: Race, availability of food frequency questionnaire, hours since last meal
CPS-II: Race
EPIC: Study center, fasting status at blood draw, time of day at blood draw; among women, menopausal status, phase of menstrual cycle, and usage of menopausal hormone therapy
JPHC: Study center, fasting status at blood draw
MEC: Race, study center, fasting status at blood draw, time of day at blood draw
NYUWHS: Race, menopausal status, number of blood draws
PHS: Smoking status
PLCO: Race
WHI: Race, latitude of clinical center
WHS: Race, fasting status at blood draw, time of day at blood draw

Covariates included in fully adjusted multivariable model:

The fully adjusted model (Model 3) included the following established and suspected colorectal cancer risk factors: body mass index (<20, 20-<22.5, 22.5-<25, 25-<27.5, 27.5-<30, ≥30 kg/m^2); physical activity (study-specific tertiles of metabolic equivalents in hours/week, if available, or low, moderate, high); race (white, black, Asian, other, for studies that did not match on race); family history of colorectal cancer (yes, no); alcohol consumption (men: 0, >0-<5, 5-<15, 15-<30, ≥30 g/d; women: 0, >0-<5, 5-<15, ≥15 g/d); smoking status (never, former, current); aspirin and/or non-steroidal anti-inflammatory drug use (yes, no for regular use); and in women, menopausal status and menopausal hormone therapy (postmenopausal/never hormone use, postmenopausal/former hormone use, postmenopausal/current hormone use, postmenopausal/missing hormone use, premenopausal, perimenopausal or missing menopausal status). For the European Prospective Investigation into Cancer and Nutrition, this variable was modeled as postmenopausal/not current hormone use and postmenopausal/current hormone use, and for the Japan Public Health Center-based Prospective Study, this variable was modeled as postmenopausal/never hormone use and postmenopausal/ever hormone use). All covariates included a missing category.

In Figure 3, condensed forms of the following covariates were used in all stratified analyses due to smaller numbers of subjects in certain strata (BMI: <25, 25-<30, ≥30 kg/m^2; alcohol consumption: in men, 0, >0-<30, ≥30 g/day; in women, 0, >0-<15, ≥15 g/day).

Covariates available for each cohort:

With the exception of aspirin/non-steroidal anti-inflammatory drug use which was only available from nine cohorts, data for most of the other covariates were available for nearly all the cohorts.

All cohorts have data on age, date of blood draw, race (data available or cohort all one race), body mass index and smoking status; 14 have physical activity (ATBC, BGS, CPS-II, EPIC, HPFS, JANUS, JPHC, MEC, NHS, NYUWHS, PHS, PLCO, WHI, and WHS); 12 have family history of colorectal cancer (ATBC, BGS, CARET, CPS-II, HPFS, JPHC, MEC, NHS, NYUWHS, PLCO, WHI, and WHS); 16 have alcohol consumption (ATBC, BGS, CARET, CLUE II, CPS-II, EPIC, HPFS, JPHC, MEC, NHS, NYUWHS, ORDET, PHS, PLCO, WHI, and WHS); 9 have aspirin/non-steroidal anti-inflammatory drug use (ATBC, CLUE II, CPS-II, HPFS, MEC, NHS, PLCO, WHI, and WHS); 12 (of 13 that included women) have menopausal status and information on menopausal hormone therapy (BGS, CLUE II, CPS-II, EPIC, JPHC, MEC, NHS, NYUWHS, ORDET, PLCO, WHI, and WHS).

Except for family history (missing for 11% of participants, 10% of women, 13% of men), the percentage of missing data for each covariate was ≤9% among the studies that measured that covariate, with most studies having ≤5% missing data. In the analyses, all covariates included a missing category.

Exclusions applied prior to analysis:

The initial sample included 6,044 case participants and 7,598 control participants. CARET women were excluded from the initial sample due to having fewer than 50 case participants. We excluded case and control participants with a missing vitamin D value (n=162), a missing date of blood draw or date of colorectal cancer diagnosis (n=24), a history of cancer before blood draw or between blood draw and case participant diagnosis date or diagnosis age (n=314), control participant blood draw after case participant diagnosis date or diagnosis age (n=22), invalid ICD code (n=93), and tumor behavior code of "malignant, metastatic site", "uncertain whether benign or malignant", or "benign" (n=208), and duplicate ID or missing matched case participant (n=6), leaving 5,706 case participants and 7,107 control participants for analysis.

Exclusions based on study-specific sample sizes:

Figure 1 and Table 3:

JPHC women and men were excluded from the <30 and 30-<40 nmol/L categories because there were no case participants in these categories. ORDET was excluded from the 75-<87.5 nmol/L category because there was only 1 case participant in this category. JPHC women and ORDET were excluded from the ≥100 nmol/L category because of small case participant numbers in this category (1 and 0 case participants, respectively).

Stratum-specific exclusions for Figure 3:

*Age at blood draw***:** CPS-II women and men and MEC women and men were excluded from the <60 years stratum because of small case participant numbers. JANUS men were excluded from the ≥60 years stratum because of small case participant numbers.

Age at diagnosis: CPS-II women and men and MEC women were excluded from the <67 years stratum because of small case participant numbers.

Race: JPHC women and men were excluded from the White stratum because there were no case and control participants in this stratum. ATBC1, ATBC2, BGS, EPIC women and men, JANUS women and men, JPHC women and men, and ORDET were excluded from the Black stratum because there were no case and control participants in this stratum. ATBC1, ATBC2, BGS, CLUE II women and men, CPS-II women, EPIC women and men, JANUS women and men, and ORDET were excluded from the Asian stratum because there were no case and control participants in this stratum.

Physical activity: CARET men, CLUE II women and men and ORDET were excluded from these analyses because this variable was not measured in these studies, and MEC women were excluded from these analyses because of small case participant numbers in all strata. JPHC women were excluded from the low stratum because of small case participant numbers. BGS was excluded from the medium stratum because of small case participant numbers. ATBC1, ATBC2, and BGS were excluded from the high stratum because of small case participant numbers.

Menopausal status: JANUS women were excluded from these analyses because this variable was not measured in this study. CPS-II women, NHS, PLCO women, and WHI were excluded from the pre-menopausal stratum because there were no case and control participants in this stratum. BGS, CLUE II women, and MEC women were excluded from the pre-menopausal stratum because of small case participant numbers.

Menopausal hormone therapy use: JANUS women were excluded from these analyses because this variable was not measured and JPHC women were excluded from these analyses because menopausal hormone therapy use was collected as ever/never. BGS, CLUE II women, and MEC women were excluded from the current stratum because of small numbers and NYUWHS and ORDET were excluded from the current stratum because all participants in these cohorts could not be current users of menopausal hormone therapy based on cohort-specific eligibility criteria.

Dietary calcium: BGS, JANUS women and men, and PHS were excluded from these analyses because this variable was not measured.

Smoking status: JPHC women were excluded from the ever smoking stratum because of small case participant numbers. CARET men were excluded from the never smoking stratum because of small case participant numbers and ATBC1 and ATBC2 were excluded from the never smoking stratum because all participants in these cohorts were smokers.

Alcohol intake: JANUS was excluded from these analyses because this variable was not measured. ATBC1, BGS, CLUE II women and men, and PHS were excluded from the no intake stratum because of small case participant numbers. BGS, JPHC women and men, MEC women, and ORDET were excluded from the low intake (women: >0-<7 g/d; men: >0-<14 g/d) stratum because of small case participant numbers. CLUE II women and men, JPHC women, MEC women, and PHS were excluded from the high intake (women: ≥7 g/d; men: ≥14 g/d) stratum because of small case participant numbers.

Season of blood draw: Summer was defined as weeks 28 to 40 and winter was defined as weeks 2 to 14. ATBC1, BGS, JANUS men, MEC women, and ORDET were excluded from the summer stratum because of small case participant numbers. JPHC women and men, MEC women, and PHS were excluded from the winter stratum because of small case participant numbers. CLUE II women and men were excluded from the winter stratum because there were no case participants.

Latitude: ATBC1, ATBC2, BGS, CLUE II women and men, EPIC women and men, JANUS women and men, ORDET, PLCO women and men were excluded from the $<35^0$ stratum because there were no participants residing in this latitude category, and CPS-II women, NYUWHS, and CARET men were excluded from the $<35^0$ stratum because of small case participant numbers. ATBC1, ATBC2, BGS, JANUS women and men, and ORDET were excluded from the $35\text{-}42^0$ stratum because there were no participants residing in this latitude category, and MEC women and men were excluded from the $35\text{-}42^0$ stratum because there were no case participants residing in this latitude category. CLUE II women and men, JPHC women and men, MEC women and men were excluded from the $>42^0$ stratum because there were no participants residing in this latitude category, and NYUWHS was excluded from the $>42^0$ stratum because of small case participant numbers.

Region: U.S. cohorts include CARET, CLUE II, CPS-II, HPFS, MEC, NHS, NYUWHS, PHS, PLCO, WHI, and WHS. Studies outside of the U.S. include ATBC1, ATBC2, BGS, EPIC, JANUS, JPHC, and ORDET.

Tumor stage: BGS was excluded from the stage I/II stratum because of small case participant numbers. BGS, JPHC men, and MEC women and men were excluded from the stage III/IV stratum because of small case participant numbers.

Tumor subsite: CARET men, JANUS women and men, MEC women and men, and PLCO women were excluded from the rectum cancer analyses because of small case participant numbers. CARET men were excluded from the proximal colon cancer analyses because of small case participant numbers. BGS, CARET men, and MEC women were excluded from the distal colon cancer analyses because of small case participant numbers.

Time to diagnosis: ATBC2, CLUE II women and men, JANUS women and men, NYUWHS, ORDET, PHS, and WHS were excluded from the ≤2 years stratum because of small case participant numbers. ATBC2, JANUS women and men, MEC women, and ORDET were excluded from the >2-5 years stratum because of small case participant numbers. BGS and MEC women and men were excluded from the >5 years stratum because of small case participant numbers.

Exclusions for **Supplementary Table 2**:

JPHC women and men were excluded from quintile 1 of all subsite analyses because there were no colorectal cancer case participants in this category. BGS and CARET men were excluded from all proximal colon cancer analyses because of small case participant numbers. BGS, CARET men, and MEC women were excluded from all distal colon cancer analyses because of small case participant numbers. CPS-II women were excluded from quintile 1 and ATBC1 was excluded from quintile 5 of the distal colon cancer analyses because of small case participant numbers in these categories. CARET men, CPS-II men, JANUS women and men, MEC women and men, and PLCO women were excluded from all rectal cancer analyses because of small case participant numbers. ORDET was excluded from quintile 5 of the rectal cancer analyses because there were no case participants in this category.

References:

1. Gail MH, Wu J, Wang M, et al. Calibration and seasonal adjustment for matched case-control studies of vitamin D and cancer. *Stat Med.* 2016;35(13):2133-2148.
2. Westgard JO, Groth T, Aronsson T, Falk H, de Verdier CH. Performance characteristics of rules for internal quality control: probabilities for false rejection and error detection. *Clin Chem.* 1977;23(10):1857-1867.

Supplementary Table 1. Comparison of Pooled Multivariable-Adjusted Relative Risks for 25(OH)D and Colorectal Cancer from 2-Stage Models Combining Study-Specific Results Using Random and Fixed Effects Models, and from 1-Stage, Aggregated Models Pooling all Primary Data.

Consortium-Wide, Sex-Specific Quintiles of Circulating 25(OH)D[*]							
			RR (95% CI)				RR (95% CI)
Model	**Q1**	**Q2**	**Q3[†]**	**Q4**	**Q5**	***P* trend[‡]**	**Q5 *vs* Q1**
Overall							
Case/control participants	1519/1421	1247/1421	1094/1423	957/1421	889/1421		
Multivariable Model[§]							
Random effects[‖]	1.15 (0.97 to 1.38)	0.98 (0.83 to 1.16)	1.00	0.92 (0.79 to 1.07)	0.78 (0.65 to 0.94)	<.001	0.68 (0.56 to 0.82)[¶]
Fixed effects	1.20 (1.04 to 1.38)	1.02 (0.89 to 1.15)	1.00	0.93 (0.81 to 1.06)	0.79 (0.69 to 0.91)	<.001	0.69 (0.58 to 0.81)[¶]
Aggregated	1.17 (1.04 to 1.32)	1.02 (0.91 to 1.14)	1.00	0.93 (0.82 to 1.05)	0.83 (0.73 to 0.94)	<.001	0.71 (0.62 to 0.81)
Women							
25(OH)D (nmol/L)	**< 37**	**37- <49**	**49- <59**	**59- <72**	**≥ 72**		
Case/control participants	822/706	654/705	574/707	476/706	422/705		
Multivariable Model[§]							
Random effects[‖]	1.21 (0.97 to 1.52)	1.00 (0.82 to 1.23)	1.00	0.83 (0.66 to 1.05)	0.67 (0.54 to 0.81)	<.001	0.56 (0.45 to 0.71)[¶]
Fixed effects	1.25 (1.03 to 1.53)	1.02 (0.86 to 1.22)	1.00	0.86 (0.71 to 1.03)	0.67 (0.54 to 0.81)	<.001	0.56 (0.45 to 0.71)[¶]
Aggregated	1.25 (1.05 to 1.48)	1.03 (0.87 to 1.20)	1.00	0.87 (0.74 to 1.03)	0.72 (0.60 to 0.86)	<.001	0.57 (0.47 to 0.69)
Men							
25(OH)D (nmol/L)	**< 41**	**41- <53**	**53- <63**	**63- <76**	**≥ 76**		
Case/control participants	697/715	593/716	520/716	481/715	467/716		
Multivariable Model[§]							
Random effects[‖]	1.12 (0.84 to 1.49)	0.98 (0.75 to 1.29)	1.00	1.01 (0.83 to 1.22)	0.93 (0.69 to 1.25)	.20	0.82 (0.61 to 1.10)[¶]
Fixed effects	1.15 (0.94 to 1.40)	1.00 (0.84 to 1.21)	1.00	1.01 (0.84 to 1.22)	0.94 (0.77 to 1.15)	.20	0.86 (0.67 to 1.09)[¶]
Aggregated	1.08 (0.91 to 1.29)	1.02 (0.86 to 1.20)	1.00	0.98 (0.83 to 1.17)	0.93 (0.78 to 1.11)	.13	0.86 (0.71 to 1.04)

Abbreviations: 25(OH)D, 25-Hydroxyvitamin D; RR, relative risk; 95% CI, 95% confidence interval; Q1-5, quintile.

[*]Consortium-wide, sex-specific quintiles are based on newly measured and calibrated season-standardized circulating 25(OH)D. Quintile cut-points are based on the distributions in the control participants separately for each sex, as shown.

[†]Quintile 3 is used as the referent category because one cohort (JPHC), with no case participants in consortium-wide quintile 1, would drop from the analysis.

[‡]*P*-value, two-sided test for trend calculated using a continuous variable based on the median 25(OH)D in each quintile.

[§]Multivariable model (equivalent to Model 3 in Table 2), conditioned on study-specific matching factors (see Supplementary Material), including date of blood draw and age, and additionally adjusted for body mass index (<20, 20-<22.5, 22.5-<25, 25-<27.5, 27.5-<30, ≥30 kg/m^2); physical activity (study-specific tertiles of metabolic equivalents in hours/week, if available, or low, moderate, high); race (white, black, Asian, other, for studies that did not match on race); family history of colorectal cancer (yes, no); alcohol consumption (men: 0, >0-<5, 5-<15, 15-<30, ≥30 g/d; women: 0, >0-<5, 5-<15, ≥15 g/d); smoking status (never, former, current); aspirin and/or non-steroidal anti-inflammatory drug use (yes, no for regular use, available for 9 cohorts only); and in women, menopausal status and menopausal hormone therapy (postmenopausal/never hormone use, postmenopausal/former hormone use, postmenopausal/current hormone use, postmenopausal/missing hormone use, premenopausal, perimenopausal or missing menopausal status). For the EPIC, this variable was modeled as postmenopausal/not current hormone use and postmenopausal/current hormone use, and for the JPHC, this was modeled as postmenopausal/never hormone use and postmenopausal/ever hormone use). All covariates included a missing category.

[‖]The results for comparison of quintiles 1, 2, 4 and 5 with quintile 3 from the 2-stage random effects model are the same as those presented in Model 3, Table 2.

[¶]Excluding one cohort (JPHC), with no case participants in consortium-wide quintile 1.

Supplementary Table 2. Pooled Associations of Sex-Specific, Consortium-Wide Quintiles of 25(OH)D with Colorectal Cancer by Subsite[*]

Consortium-Wide, Sex-Specific Quintiles of Circulating 25(OH)D[†]									
Model	**Q1**	**Q2**	**RR (95% CI) Q3[‡]**	**Q4**	**Q5**	***P* trend[§]**	***P* Het by Study[‖]**	***P* Het by Sex[¶]**	***P* Common Effects by Subsite**
Colon Cancer									
Overall									
Case/control participants	1,067/992	889/1,024	811/1,018	703/1,065	696/1,073				
Multivariable model[††]	1.12 (0.92 to 1.37)	0.93 (0.77 to 1.14)	1.00	0.85 (0.70 to 1.03)	0.79 (0.65 to 0.96)	.001	.16, .13	.36, .05	.19, .62[#]
Women									
25(OH)D (nmol/L)	**< 37**	**37- <49**	**49- <59**	**59- <72**	**≥ 72**				
Case/control participants	614/518	493/538	430/517	365/540	344/570				
Multivariable model[††]	1.27 (1.01 to 1.60)	0.98 (0.76 to 1.26)	1.00	0.79 (0.59 to 1.06)	0.66 (0.53 to 0.83)	<.001	.48, .85		.73, .74[#]
Men									
25(OH)D (nmol/L)	**< 41**	**41- <53**	**53- <63**	**63- <76**	**≥ 76**				
Case/control participants	453/474	396/486	381/501	338/525	352/503				
Multivariable model[††]	1.01 (0.73 to 1.40)	0.89 (0.65 to 1.22)	1.00	0.91 (0.71 to 1.16)	0.93 (0.67 to 1.29)	.46	.08, .04		.16, .68[#]
Proximal Colon									
Overall									
Case/control participants	518/490	453/498	441/528	357/561	364/616				
Multivariable model[††]	1.05 (0.78 to 1.41)	0.88 (0.68 to 1.14)	1.00	0.78 (0.57 to 1.06)	0.65 (0.48 to 0.90)	<.001	.16, .05	.76, .03	.38, .11**
Women									
25(OH)D nmol/L	**< 37**	**37- <49**	**49- <59**	**59- <72**	**≥ 72**				
Case/control participants	326/297	276/294	258/284	195/309	198/352				
Multivariable model[††]	1.00 (0.67 to 1.50)	0.77 (0.52 to 1.12)	1.00	0.65 (0.42 to 1.00)	0.49 (0.31 to 0.76)	<.001	.20, .12		.30, .14**
Men									
25(OH)D (nmol/L)	**< 41**	**41- <53**	**53- <63**	**63- <76**	**≥ 76**				
Case/control participants	192/193	177/204	183/244	162/252	166/264				
Multivariable model[††]	1.09 (0.68 to 1.75)	0.99 (0.71 to 1.40)	1.00	0.94 (0.60 to 1.47)	0.89 (0.59 to 1.34)	.06	.19, .24		.87, .46**
Distal Colon									
Overall									
Case/control participants	409/384	329/398	272/393	280/418	261/376				
Multivariable model[††]	1.31 (0.88 to 1.95)	1.09 (0.80 to 1.49)	1.00	1.01 (0.76 to 1.34)	0.97 (0.68 to 1.39)	.13	.14, .20	.38, .34	
Women									
25(OH)D (nmol/L)	**< 37**	**37- <49**	**49- <59**	**59- <72**	**≥ 72**				
Case/control participants	215/180	171/181	129/185	136/186	108/168				
Multivariable model[††]	1.48 (0.79 to 2.78)	1.27 (0.83 to 1.94)	1.00	1.02 (0.66 to 1.58)	0.80 (0.49 to 1.30)	.01	.15, .60		
Men									
25(OH)D nmol/L	**< 41**	**41- <53**	**53- <63**	**63- <76**	**≥ 76**				
Case/control participants	194/204	158/217	143/208	144/232	153/208				
Multivariable model[††]	1.16 (0.69 to 1.96)	0.96 (0.61 to 1.52)	1.00	1.00 (0.69 to 1.45)	1.15 (0.66 to 1.99)	.97	.24, .07		
Rectal Cancer									
Overall									
Case/control participants	423/398	318/356	255/372	222/309	149/275				
Multivariable model[††]	1.44 (1.05 to 1.98)	1.11 (0.79 to 1.55)	1.00	1.12 (0.78 to 1.59)	0.88 (0.61 to 1.27)	.01	.66, .40	.90, .25	
Women									
25(OH)D (nmol/L)	**< 37**	**37- <49**	**49- <59**	**59- <72**	**≥ 72**				
Case/control participants	195/177	145/154	133/176	105/151	63/119				
Multivariable model[††]	1.41 (0.84 to 2.36)	0.88 (0.45 to 1.74)	1.00	0.87 (0.44 to 1.72)	0.58 (0.26 to 1.26)	.02	.48, .19		
Men									
25(OH)D (nmol/L)	**< 41**	**41- <53**	**53- <63**	**63- <76**	**≥ 76**				
Case/control participants	228/221	173/202	122/196	117/158	86/156				
Multivariable model[††]	1.46 (0.98 to 2.18)	1.18 (0.81 to 1.71)	1.00	1.34 (0.89 to 2.02)	1.05 (0.67 to 1.65)	.22	.58, .75		

Abbreviations: 25(OH)D, 25-Hydroxyvitamin D; RR, relative risk; 95% CI, 95% confidence interval; Q1-5, quintile; Het, heterogeneity.

[*]Colon cancer was defined using International Classification of Diseases Oncology (ICD-O) codes: C18.0, C18.2–C18.9, with cecum, ascending colon, hepatic flexure, transverse colon and splenic flexure comprising proximal colon and descending and sigmoid colon comprising distal colon. Cancers of the recto-sigmoid junction (C19.9) and rectum (C20.9) comprised cancers of the rectum.

[†]Consortium-wide, sex-specific quintiles are based on newly measured and calibrated season-standardized circulating 25(OH)D. Quintile cut-points are based on the distributions in the control participants, separately for each sex, as shown.

[‡]Quintile 3 is used as the referent category because one cohort (JPHC), with no case participants in consortium-wide quintile 1, would drop from the analysis.
[§]*P*-value, two-sided test for trend calculated using a continuous variable based on the median 25(OH)D in each quintile.
[|]*P*-value, two-sided test for between-study heterogeneity. Results are for quintile 1 and quintile 5, respectively.
[¶]*P*-value, two-sided test for between-study heterogeneity due to sex. Results are for quintile 1 and quintile 5, respectively.
[#]*P*-value, two-sided test for common effects by subsite for colon *vs* rectum cancer. Results are for quintile 1 and quintile 5, respectively.
[**]*P*-value, two-sided test for common effects by subsite for proximal *vs* distal colon cancer. Results are for quintile 1 and quintile 5, respectively.
[††]This model is similar to model 3 in Table 2, conditioned on study-specific matching factors (see Supplemental Material), including date of blood draw and age, and additionally adjusted for body mass index (<25, 25-<30, ≥30 kg/m^2); physical activity (study-specific tertiles of metabolic equivalents in hours/week, if available, or low, moderate, high); race (white, black, Asian, other, for studies that did not match on race); family history of colorectal cancer (yes, no); alcohol consumption (men: 0, >0-<30, ≥30 g/d; women: 0, >0-<15, ≥15 g/d); smoking status (never, former, current); aspirin and/or non-steroidal anti-inflammatory drug use (yes, no for regular use, available for 9 cohorts only); and in women, menopausal status and menopausal hormone therapy (postmenopausal/never hormone use, postmenopausal/former hormone use, postmenopausal/current hormone use, postmenopausal/missing hormone use, premenopausal, perimenopausal or missing menopausal status). For the EPIC, this variable was modeled as postmenopausal/not current hormone use and postmenopausal/current hormone use, and for the JPHC, this was modeled as postmenopausal/never hormone use and postmenopausal/ever hormone use). All covariates included a missing category.