



Supplementary Figure1 Flow chart of the study population in the Nurses' Health Study (1980-2012) and Health Professionals Follow-up Study (1986-2012)

Supplementary Table 1. Age-adjusted characteristics of cases by T-cell subsets availability in the combined study.

	T-cell subsets unavailable cases (n=2,343)	T-cell subsets available cases (n=736)
Age, years	67.8(9.6)	67.7(9.2)
Total calcium intake, mg/day	924(371)	911(333)
Dietary calcium intake, mg/day	749(238)	760(250)
Supplemental calcium intake, mg/day	180(273)	155(225)
Dairy calcium intake, mg/day	435(229)	447(242)
White, %	97.2	97.1
Body mass index, kg/m ²	26.0(4.2)	25.9(4.2)
Activity, METS-hours/week	20.1(23.4)	18.7(22.0)
Family history of colorectal cancer, %	17.8	20.9
Regular aspirin use (2 or more tablets/week), %	35.2	41.1
Past smoking, %	35.6	33.6
Current smoking, %	22.1	24.4
Multivitamin use, %	43.9	44.1
History of sigmoidoscopy/endoscopy, %	26.4	21.7
Total energy intake, kcal/day	1793(514)	1814(494)
Alcohol, g/day	9.2(12.9)	9.5(13.7)
Total folate intake, µg/day	471(222)	443(199)
Total vitamin D, IU/day	380(227)	368(230)
Red meat, servings/week	1.9(1.4)	1.9(1.3)
Processed meat, servings/week	1.1(1.5)	1.0(1.1)
Total fat, g/day	64.8(12.3)	63.9(11.9)
Total fiber, g/day	19.6(5.9)	19.5(5.6)
ω-3 polyunsaturated fatty acids, g/day	0.3(0.2)	0.3(0.2)
ω-6 polyunsaturated fatty acids, g/day	9.5(3.1)	9.4(3.2)

Supplementary Table 2. Total calcium intake and risk of colorectal cancer according to densities of tumor-infiltrating T-cell subsets in the Nurses' Health Study (1980-2012)

	Total calcium intake (mg/d)					P _{trend} *	
	<600	600-799	800-999	1000-1199	≥1200		
Total colorectal cancer							
Person-years (n=2,602,860)	460,811	593,722	562,128	439,470	546,729		
No. cases (n=472)	71	122	119	80	80		
Age-adjusted HR (95%CI)	1 (ref)	1.01 (0.82-1.48)	1.07 (0.79-1.44)	0.89 (0.65-1.24)	0.70 (0.51-0.98)	0.004	
Multivariable HR (95%CI)	1 (ref)	1.10 (0.81-1.49)	1.08 (0.78-1.49)	0.95 (0.66-1.36)	0.82 (0.56-1.20)	0.13	
CD3⁺							
Low							
No. cases (n=227)	46	64	44	41	32		
Age-adjusted HR (95% CI)	1 (ref)	0.89 (0.61-1.31)	0.63 (0.41-0.96)	0.74 (0.48-1.13)	0.46 (0.29-0.73)	0.0004	0.10
Multivariable HR (95% CI)§	1 (ref)	0.87 (0.59-1.29)	0.62 (0.40-0.96)	0.76 (0.48-1.20)	0.52 (0.32-0.86)	0.01	0.09
High							
No. cases (n=218)	23	54	68	32	41		
Age-adjusted HR (95% CI)	1 (ref)	1.49 (0.91-2.43)	1.81 (1.12-2.92)	1.05 (0.61-1.81)	1.04 (0.62-1.75)	0.24	
Multivariable HR (95% CI)§	1 (ref)	1.49 (0.90-2.44)	1.79 (1.09-2.94)	1.10 (0.63-1.94)	1.18 (0.68-2.07)	0.63	
CD8⁺							
Low							
No. cases (n=239)	41	64	61	41	32		
Age-adjusted HR (95%CI)	1 (ref)	0.97 (0.65-1.44)	0.90 (0.60-1.34)	0.74 (0.48-1.15)	0.45 (0.28-0.72)	0.0001	0.01
Multivariable HR (95% CI)§	1 (ref)	0.95 (0.63-1.42)	0.88 (0.58-1.34)	0.76 (0.48-1.22)	0.51 (0.31-0.85)	0.004	0.01
High							
No. cases (n=206)	25	52	54	33	42		
Age-adjusted HR (95%CI)	1 (ref)	1.38 (0.85-2.23)	1.46 (0.90-2.36)	1.13 (0.66-1.91)	1.16 (0.70-1.92)	0.84	
Multivariable HR (95% CI)§	1 (ref)	1.37 (0.84-2.22)	1.43 (0.87-2.35)	1.17 (0.67-2.03)	1.32 (0.77-2.27)	0.70	
CD45RO⁺							
Low							
No. cases (n=200)	38	54	48	32	28		
Age-adjusted HR (95%CI)	1 (ref)	0.87 (0.57-1.32)	0.78 (0.51-1.20)	0.64 (0.40-1.04)	0.44 (0.27-0.73)	0.0004	0.02
Multivariable HR (95% CI)§	1 (ref)	0.85 (0.56-1.30)	0.77 (0.49-1.21)	0.66 (0.40-1.10)	0.50 (0.29-0.86)	0.006	0.02
High							
No. cases (n=254)	29	64	67	44	50		
Age-adjusted HR (95%CI)	1 (ref)	1.47 (0.94-2.28)	1.51 (0.97-2.35)	1.23 (0.76-1.98)	1.10 (0.69-1.76)	0.55	
Multivariable HR (95% CI)§	1 (ref)	1.46 (0.93-2.28)	1.50 (0.95-2.37)	1.29 (0.78-2.13)	1.26 (0.76-2.09)	0.91	

FOXP3*							
Low							
No. cases (n=211)	37	46	61	37	30		
Age-adjusted HR (95%CI)	1 (ref)	0.80 (0.52-1.23)	1.04 (0.69-1.58)	0.79 (0.50-1.26)	0.51 (0.31-0.84)	0.01	0.23
Multivariable HR (95% CI)§	1 (ref)	0.79 (0.51-1.23)	1.04 (0.67-1.60)	0.83 (0.51-1.36)	0.60 (0.35-1.01)	0.09	0.22
High							
No. cases (n=228)	29	63	49	41	46		
Age-adjusted HR (95%CI)	1 (ref)	1.39 (0.89-2.17)	1.08 (0.68-1.72)	1.11 (0.68-1.80)	0.97 (0.60-1.56)	0.33	
Multivariable HR (95% CI)§	1 (ref)	1.37 (0.87-2.15)	1.06 (0.65-1.71)	1.16 (0.69-1.93)	1.13 (0.67-1.90)	0.86	

CI, confidence interval; HR, hazard ratio.

Duplication-method Cox proportional cause-specific hazards regression for competing risks data was used to compute HRs and 95% CIs.

All analyses were stratified by age (in month) and year of questionnaire return.

*: Linear trend test using the median intake of each category.

¶: The likelihood ratio test was used to test for the heterogeneity of the association between total calcium intake and colorectal cancer risk by densities of tumor-infiltrating T-cell subsets.

§: Multivariable hazard ratios were adjusted for **age** (in month), **race** (Caucasian vs. non-Caucasian), **adult BMI** (< 25, 25 -< 27.5, 27.5 -< 30, or ≥ 30 kg/m²), smoking (0, 1-10, or > 10 pack-years), **history of colorectal cancer in a parent or sibling** (yes or no), **history of sigmoidoscopy/colonoscopy** (yes or no), **physical activity** (< 3, 3-< 27, ≥ 27 MET-hrs/wk), **regular aspirin use** (yes, no), **alcohol consumption** (0 -< 5, 5 -< 15, or ≥ 15 g/d), energy-adjusted total intake of **folate**, **vitamin D**, **red meat** and **processed meat** (all in tertiles).

Supplementary Table 3. Total calcium intake and risk of colorectal cancer according to densities of tumor-infiltrating T-cell subsets in the Health Professionals Follow-up Study (1986-2012)

	Total calcium intake (mg/d)					P _{trend} *	P _{heterogeneity} ††
	<600	600-799	800-999	1000-1199	≥1200		
Total colorectal cancer							
Person-years (n=1,060,180)	156,527	296,128	247,236	156,721	203,568		
No. cases (n=264)	45	85	57	41	36		
Age-adjusted HR (95%CI)	1 (ref)	1.10 (0.76-1.58)	0.88 (0.59-1.31)	1.05 (0.68-1.60)	0.64 (0.41-1.00)	0.02	
Multivariable HR (95%CI)	1 (ref)	1.17 (0.80-1.70)	0.98 (0.64-1.49)	1.19 (0.75-1.89)	0.77 (0.47-1.27)	0.22	
CD3⁺							
Low							
No. cases (n=120)	18	39	29	17	17		
Age-adjusted HR (95% CI)	1 (ref)	1.32 (0.75-2.33)	1.20 (0.66-2.17)	1.15 (0.59-2.25)	0.80 (0.41-1.56)	0.25	0.50
Multivariable HR (95% CI)§	1 (ref)	1.38 (0.78-2.44)	1.31 (0.71-2.41)	1.29 (0.64-2.58)	0.91 (0.45-1.85)	0.52	0.58
High							
No. cases (n=132)	25	44	23	24	16		
Age-adjusted HR (95% CI)	1 (ref)	0.96 (0.59-1.58)	0.62 (0.35-1.09)	1.04 (0.59-1.84)	0.49 (0.26-0.93)	0.04	
Multivariable HR (95% CI)§	1 (ref)	1.04 (0.63-1.72)	0.69 (0.38-1.24)	1.19 (0.66-2.17)	0.60 (0.31-1.18)	0.17	
CD8⁺							
Low							
No. cases (n=100)	18	29	25	14	14		
Age-adjusted HR (95%CI)	1 (ref)	0.92 (0.51-1.67)	0.93 (0.50-1.71)	0.83 (0.41-1.69)	0.59 (0.29-1.19)	0.12	0.85
Multivariable HR (95% CI)§	1 (ref)	0.96 (0.53-1.76)	1.01 (0.54-1.89)	0.92 (0.44-1.92)	0.69 (0.33-1.44)	0.30	0.83
High							
No. cases (n=138)	22	52	25	24	15		
Age-adjusted HR (95%CI)	1 (ref)	1.36 (0.82-2.25)	0.81 (0.45-1.45)	1.32 (0.73-2.37)	0.57 (0.29-1.10)	0.04	
Multivariable HR (95% CI)§	1 (ref)	1.44 (0.86-2.41)	0.89 (0.49-1.62)	1.47 (0.79-2.72)	0.66 (0.33-1.33)	0.14	
CD45RO⁺							
Low							
No. cases (n=148)	27	44	32	25	20		
Age-adjusted HR (95%CI)	1 (ref)	0.96 (0.59-1.56)	0.85 (0.51-1.43)	1.05 (0.60-1.83)	0.60 (0.33-1.07)	0.11	0.60
Multivariable HR (95% CI)§	1 (ref)	1.03 (0.63-1.69)	0.95 (0.56-1.63)	1.22 (0.68-2.18)	0.71 (0.38-1.34)	0.35	0.68
High							
No. cases (n=105)	18	37	22	16	12		
Age-adjusted HR (95%CI)	1 (ref)	1.16 (0.66-2.05)	0.82 (0.43-1.56)	1.03 (0.52-2.05)	0.53 (0.26-1.11)	0.05	
Multivariable HR (95% CI)§	1 (ref)	1.25 (0.70-2.22)	0.93 (0.49-1.80)	1.19 (0.59-2.40)	0.67 (0.31-1.44)	0.20	

FOXP3⁺							
Low							
No. cases (n=125)	24	43	28	18	12		
Age-adjusted HR (95%CI)	1 (ref)	1.07 (0.64-1.77)	0.86 (0.49-1.50)	0.84 (0.45-1.56)	0.40 (0.20-0.80)	0.004	0.08
Multivariable HR (95% CI)§	1 (ref)	1.16 (0.69-1.94)	0.98 (0.55-1.74)	0.98 (0.51-1.89)	0.49 (0.24-1.03)	0.03	0.09
High							
No. cases (n=109)	16	32	25	18	18		
Age-adjusted HR (95%CI)	1 (ref)	1.14 (0.62-2.08)	1.01 (0.53-1.90)	1.31 (0.66-2.60)	0.87 (0.44-1.72)	0.66	
Multivariable HR (95% CI)§	1 (ref)	1.22 (0.66-2.26)	1.13 (0.59-2.19)	1.48 (0.73-3.01)	1.05 (0.51-2.16)	0.95	

CI, confidence interval; HR, hazard ratio.

Duplication-method Cox proportional cause-specific hazards regression for competing risks data was used to compute HRs and 95% CIs.

All analyses were stratified by age (in month) and year of questionnaire return.

*: Linear trend test using the median intake of each category.

¶: The likelihood ratio test was used to test for the heterogeneity of the association between total calcium intake and colorectal cancer risk by densities of tumor-infiltrating T-cell subsets.

§: Multivariable hazard ratios were adjusted for **age** (in month), **race** (Caucasian vs. non-Caucasian), **adult BMI** (< 25, 25 -< 27.5, 27.5 -< 30, or ≥ 30 kg/m²), smoking (0, 1-10, or > 10 pack-years), **history of colorectal cancer in a parent or sibling** (yes or no), **history of sigmoidoscopy/colonoscopy** (yes or no), **physical activity** (< 3, 3-< 27, ≥ 27 MET-hrs/wk), **regular aspirin use** (yes, no), **alcohol consumption** (0 -< 5, 5 -< 15, or ≥ 15 g/d), energy-adjusted total intake of **folate**, **vitamin D**, **red meat** and **processed meat** (all in tertiles).

Supplementary Table 4. Total calcium intake and risk of colorectal cancer according to densities of tumor-infiltrating T-cell subsets in the Nurses' Health Study (1980-2012) and Health Professionals Follow-up Study (1986-2012) by anatomic subsites

	Total calcium intake (mg/d)					<i>P</i> -trend*	<i>P</i> -heterogeneity ††
	<600	600-799	800-999	1000-1199	≥1200		
Colon cancer							
Person-years (n=3,663,214)	617,361	889,901	809,445	596,194	750,313		
No. cases (n=588)	91	165	145	98	89		
Multivariable HR (95% CI)§	1 (ref)	1.12 (0.86-1.47)	1.06 (0.80-1.42)	1.00 (0.73-1.38)	0.76 (0.54-1.06)	0.03	
CD3⁺							
Low							
No. cases (n=279)	50	83	62	46	38		
Multivariable HR (95% CI)§	1 (ref)	1.03 (0.72-1.48)	0.84 (0.57-1.24)	0.87 (0.57-1.34)	0.60 (0.38-0.96)	0.01	0.34
High							
No. cases (n=276)	37	78	72	45	44		
Multivariable HR (95% CI)§	1 (ref)	1.27 (0.85-1.90)	1.25 (0.82-1.89)	1.08 (0.68-1.72)	0.86 (0.54-1.39)	0.19	
CD8⁺							
Low							
No. cases (n=263)	45	75	67	42	34		
Multivariable HR (95% CI)§	1 (ref)	0.99 (0.67-1.44)	0.90 (0.60-1.33)	0.75 (0.48-1.18)	0.51 (0.32-0.83)	0.001	0.05
High							
No. cases (n=280)	36	83	67	50	44		
Multivariable HR (95% CI)§	1 (ref)	1.42 (0.96-2.12)	1.27 (0.83-1.95)	1.36 (0.86-2.14)	0.98 (0.61-1.58)	0.42	
CD45RO⁺							
Low							
No. cases (n=265)	49	72	61	47	36		
Multivariable HR (95% CI)§	1 (ref)	0.89 (0.61-1.29)	0.84 (0.56-1.24)	0.90 (0.59-1.38)	0.57 (0.36-0.90)	0.02	0.32
High							
No. cases (n=299)	38	87	77	47	50		
Multivariable HR (95% CI)§	1 (ref)	1.44 (0.97-2.12)	1.33 (0.88-2.00)	1.11 (0.71-1.75)	0.98 (0.62-1.56)	0.26	
FOXP3⁺							
Low							
No. cases (n=256)	49	67	69	42	29		
Multivariable HR (95% CI)§	1 (ref)	0.84 (0.57-1.22)	0.93 (0.63-1.38)	0.77 (0.50-1.20)	0.45 (0.27-0.73)	0.002	0.02
High							

No. cases (n=280)	33	80	66	51	50		
Multivariable HR (95% CI)§	1 (ref)	1.50 (0.99-2.27)	1.27 (0.82-1.97)	1.39 (0.87-2.21)	1.14 (0.71-1.85)	0.77	
Proximal colon cancer							
Person-years (n=3,663,424)	617,402	889,960	809,488	596,223	750,351		
No. cases (n=356)	47	103	98	60	48		
Multivariable HR (95% CI)§	1 (ref)	1.28 (0.90-1.83)	1.27 (0.87-1.85)	1.03 (0.68-1.57)	0.67 (0.43-1.06)	0.008	
CD3⁺							
Low							
No. cases (n=167)	24	52	42	28	21		
Multivariable HR (95% CI)§	1 (ref)	1.25 (0.76-2.06)	1.06 (0.62-1.79)	0.98 (0.55-1.75)	0.58 (0.31-1.09)	0.02	0.73
High							
No. cases (n=169)	21	47	50	28	23		
Multivariable HR (95% CI)§	1 (ref)	1.30 (0.77-2.19)	1.41 (0.82-2.41)	1.02 (0.56-1.85)	0.68 (0.36-1.30)	0.05	
CD8⁺							
Low							
No. cases (n=165)	25	55	44	24	17		
Multivariable HR (95% CI)§	1 (ref)	1.25 (0.77-2.02)	0.98 (0.58-1.64)	0.69 (0.38-1.26)	0.41 (0.21-0.79)	0.0002	0.01
High							
No. cases (n=168)	18	44	47	32	27		
Multivariable HR (95% CI)§	1 (ref)	1.43 (0.82-2.50)	1.62 (0.91-2.87)	1.49 (0.81-2.76)	1.00 (0.52-1.90)	0.51	
CD45RO⁺							
Low							
No. cases (n=154)	23	50	43	23	15		
Multivariable HR (95% CI)§	1 (ref)	1.25 (0.75-2.07)	1.13 (0.66-1.93)	0.81 (0.44-1.49)	0.43 (0.22-0.86)	0.001	0.06
High							
No. cases (n=187)	23	48	51	34	31		
Multivariable HR (95% CI)§	1 (ref)	1.23 (0.74-2.04)	1.32 (0.79-2.22)	1.15 (0.66-2.03)	0.85 (0.47-1.53)	0.27	
FOXP3⁺							
Low							
No. cases (n=152)	26	39	48	22	17		
Multivariable HR (95% CI)§	1 (ref)	0.86 (0.52-1.44)	1.11 (0.67-1.85)	0.67 (0.37-1.23)	0.42 (0.22-0.81)	0.004	0.10
High							
No. cases (n=170)	15	51	43	35	26		
Multivariable HR (95% CI)§	1 (ref)	1.96 (1.09-3.52)	1.64 (0.89-3.01)	1.79 (0.95-3.38)	1.11 (0.56-2.19)	0.38	
Distal colon cancer							

Person-years (n=3,663,566)	617,411	890,003	809,540	596,252	750,360		
No. cases (n=223)	43	58	45	36	41		
Multivariable HR (95% CI)§	1 (ref)	0.92 (0.61-1.38)	0.80 (0.50-1.26)	0.94 (0.57-1.55)	0.92(0.55-1.52)	0.87	
CD3⁺							
Low							
No. cases (n=107)	25	29	19	17	17		
Multivariable HR (95% CI)§	1 (ref)	0.82 (0.47-1.42)	0.61 (0.33-1.15)	0.78 (0.40-1.51)	0.70 (0.35-1.38)	0.35	0.33
High							
No. cases (n=103)	16	29	21	16	21		
Multivariable HR (95% CI)§	1 (ref)	1.14 (0.61-2.13)	0.93 (0.47-1.83)	1.08 (0.52-2.25)	1.15 (0.56-2.35)	0.76	
CD8⁺							
Low							
No. cases (n=93)	19	19	21	17	17		
Multivariable HR (95% CI)§	1 (ref)	0.63 (0.33-1.21)	0.74 (0.38-1.42)	0.84 (0.42-1.71)	0.71 (0.34-1.47)	0.70	0.97
High							
No. cases (n=108)	18	36	20	17	17		
Multivariable HR (95% CI)§	1 (ref)	1.35 (0.75-2.41)	0.88 (0.45-1.71)	1.13 (0.55-2.30)	0.98 (0.47-2.03)	0.65	
CD45RO⁺							
Low							
No. cases (n=109)	25	22	18	23	21		
Multivariable HR (95% CI)§	1 (ref)	0.59 (0.33-1.06)	0.56 (0.30-1.07)	1.06 (0.57-1.97)	0.80 (0.42-1.53)	0.80	0.60
High							
No. cases (n=105)	15	35	24	12	19		
Multivariable HR (95% CI)§	1 (ref)	1.63 (0.87-3.02)	1.20 (0.60-2.37)	0.87 (0.39-1.93)	1.19 (0.56-2.50)	0.67	
FOXP3⁺							
Low							
No. cases (n=100)	23	25	20	20	12		
Multivariable HR (95% CI)§	1 (ref)	0.72 (0.40-1.29)	0.66 (0.35-1.24)	0.92 (0.48-1.76)	0.48 (0.22-1.02)	0.16	0.14
High							
No. cases (n=106)	18	28	22	14	24		
Multivariable HR (95% CI)§	1 (ref)	1.05 (0.57-1.94)	0.88 (0.45-1.71)	0.84 (0.40-1.78)	1.24 (0.62-2.47)	0.63	
Rectal cancer							
Person-years (n=3,663,621)	617,427	890,019	809,549	596,258	750,368		
No. cases (n=148)	25	42	31	23	27		

Multivariable HR (95% CI)§	1 (ref)	1.11 (0.66-1.85)	0.96 (0.54-1.69)	1.06 (0.56-1.99)	1.01 (0.53-1.93)	0.91	
CD3⁺							
Low							
No. cases (n=68)	14	20	11	12	11		
Multivariable HR (95% CI)§	1 (ref)	0.98 (0.49-1.98)	0.66 (0.29-1.50)	0.99 (0.43-2.28)	0.73 (0.31-1.74)	0.47	0.65
High							
No. cases (n=74)	11	20	19	11	13		
Multivariable HR (95% CI)§	1 (ref)	1.14 (0.54-2.41)	1.21 (0.56-2.64)	1.07 (0.44-2.60)	1.00 (0.41-2.41)	0.87	
CD8⁺							
Low							
No. cases (n=76)	14	18	19	13	12		
Multivariable HR (95% CI)§	1 (ref)	0.84 (0.41-1.72)	1.04 (0.50-2.16)	1.00 (0.44-2.27)	0.74 (0.31-1.73)	0.63	0.72
High							
No. cases (n=64)	11	21	12	7	13		
Multivariable HR (95% CI)§	1 (ref)	1.30 (0.61-2.74)	0.86 (0.37-2.03)	0.78 (0.29-2.12)	1.22 (0.50-2.97)	0.99	
CD45RO⁺							
Low							
No. cases (n=83)	16	26	19	10	12		
Multivariable HR (95% CI)§	1 (ref)	1.02 (0.53-1.93)	0.89 (0.44-1.81)	0.67 (0.29-1.55)	0.65 (0.28-1.49)	0.17	0.07
High							
No. cases (n=60)	9	14	12	13	12		
Multivariable HR (95% CI)§	1 (ref)	1.08 (0.46-2.53)	1.05 (0.43-2.58)	1.80 (0.73-4.43)	1.34 (0.52-3.42)	0.35	
FOXP3⁺							
Low							
No. cases (n=80)	12	22	20	13	13		
Multivariable HR (95% CI)§	1 (ref)	1.34 (0.65-2.75)	1.42 (0.67-3.02)	1.34 (0.58-3.12)	1.14 (0.48-2.73)	0.89	0.93
High							
No. cases (n=57)	12	15	8	8	14		
Multivariable HR (95% CI)§	1 (ref)	0.77 (0.35-1.68)	0.49 (0.19-1.24)	0.77 (0.30-2.00)	1.00 (0.42-2.37)	0.83	

CI, confidence interval; HR, hazard ratio.

Duplication-method Cox proportional cause-specific hazards regression for competing risks data was used to compute HRs and 95% CIs.

All analyses were stratified by age (in month), year of questionnaire return and sex.

*: Linear trend test using the median intake of each category.

¶: The likelihood ratio test was used to test for the heterogeneity of the association between total calcium intake and colorectal cancer risk by densities of tumor-infiltrating T-cell subsets.

§: Multivariable hazard ratios were adjusted for **age** (in month), **race** (Caucasian vs. non-Caucasian), **adult BMI** (< 25, 25 -< 27.5, 27.5 -< 30, or ≥ 30 kg/m²), smoking (0, 1-10, or > 10 pack-years), **history of colorectal cancer in a parent or sibling** (yes or no), **history of sigmoidoscopy/colonoscopy** (yes or no), **physical activity** (< 3, 3-< 27, ≥ 27 MET-hrs/wk), **regular aspirin use** (yes, no), **alcohol consumption** (0 -< 5, 5 -< 15, or ≥ 15 g/d), energy-adjusted total intake of **folate**, **vitamin D**, **red meat** and **processed meat** (all in tertiles).

Supplementary Table 5. Total calcium intake and risk of colorectal cancer according to microsatellite instability and densities of tumor-infiltrating T-cell subsets in the Nurses' Health Study (1980-2012) and Health Professionals Follow-up Study (1986-2012)

	Total calcium intake (mg/d)					P _{trend} *	P _{heterogeneity} †
	<600	600-799	800-999	1000-1199	≥1200		
Microsatellite instability							
Non-MSI-High							
CD3⁺							
Low							
No. cases (n=294)	52	91	62	49	40		
Age-adjusted HR (95% CI)	1 (ref)	1.11 (0.79-1.56)	0.82 (0.57-1.19)	0.89 (0.60-1.33)	0.55 (0.36-0.84)	0.0008	0.76
Multivariable HR (95% CI)§	1 (ref)	1.12 (0.79-1.58)	0.85 (0.58-1.25)	0.96 (0.63-1.45)	0.64 (0.41-0.99)	0.01	0.76
High							
No. cases (n=279)	38	83	69	43	46		
Age-adjusted HR (95% CI)	1 (ref)	1.30 (0.88-1.92)	1.16 (0.78-1.74)	1.00 (0.64-1.56)	0.81 (0.52-1.26)	0.06	
Multivariable HR (95% CI)§	1 (ref)	1.34 (0.91-1.99)	1.21 (0.80-1.83)	1.08 (0.68-1.71)	0.95 (0.60-1.51)	0.29	
MSI-High							
CD3⁺							
Low							
No. cases (n=52)	12	11	11	9	9		
Age-adjusted HR (95% CI)	1 (ref)	0.56 (0.25-1.29)	0.62 (0.27-1.43)	0.67 (0.28-1.60)	0.54 (0.22-1.30)	0.32	
Multivariable HR (95% CI)§	1 (ref)	0.58 (0.25-1.32)	0.62 (0.27-1.44)	0.70 (0.29-1.70)	0.61 (0.25-1.49)	0.46	
High							
No. cases (n=58)	9	13	17	11	8		
Age-adjusted HR (95% CI)	1 (ref)	0.87 (0.37-2.04)	1.10 (0.49-2.49)	0.88 (0.36-2.15)	0.47 (0.18-1.24)	0.12	
Multivariable HR (95% CI)§	1 (ref)	0.90 (0.38-2.11)	1.16 (0.51-2.64)	0.99 (0.40-2.44)	0.57 (0.22-1.53)	0.27	
Microsatellite instability							
Non-MSI-High							
CD8⁺							
Low							
No. cases (n=280)	46	80	70	44	40		
Age-adjusted HR (95% CI)	1 (ref)	1.05 (0.73-1.51)	0.94 (0.65-1.37)	0.79 (0.52-1.20)	0.54 (0.35-0.83)	0.0006	0.12
Multivariable HR (95% CI)§	1 (ref)	1.06 (0.73-1.53)	0.97 (0.65-1.42)	0.84 (0.54-1.29)	0.63 (0.40-0.99)	0.01	0.11
High							
No. cases (n=281)	39	89	63	47	43		

Age-adjusted HR (95% CI)	1 (ref)	1.43 (0.98-2.10)	1.14 (0.76-1.71)	1.21 (0.79-1.87)	0.85 (0.55-1.32)	0.10	
Multivariable HR (95% CI)§	1 (ref)	1.47 (1.00-2.15)	1.18 (0.78-1.79)	1.29 (0.83-2.02)	0.97 (0.61-1.55)	0.35	
MSI-High							
CD8⁺							
Low							
No. cases (n=52)	13	11	15	9	4		
Age-adjusted HR (95% CI)	1 (ref)	0.53 (0.24-1.19)	0.75 (0.35-1.60)	0.56 (0.24-1.33)	0.19 (0.06-0.60)	0.01	
Multivariable HR (95% CI)§	1 (ref)	0.54 (0.24-1.21)	0.75 (0.35-1.61)	0.59 (0.25-1.40)	0.22 (0.07-0.69)	0.02	
High							
No. cases (n=56)	7	14	12	10	13		
Age-adjusted HR (95% CI)	1 (ref)	1.15 (0.46-2.87)	1.02 (0.40-2.63)	1.10 (0.41-2.93)	1.08 (0.42-2.76)	0.97	
Multivariable HR (95% CI)§	1 (ref)	1.19 (0.47-2.96)	1.05 (0.41-2.72)	1.21 (0.45-3.25)	1.28 (0.49-3.31)	0.66	
Microsatellite instability							
Non-MSI-High							
CD45RO⁺							
Low							
No. cases (n=307)	54	91	71	51	40		
Age-adjusted HR (95% CI)	1 (ref)	1.02 (0.72-1.43)	0.86 (0.60-1.23)	0.85 (0.58-1.25)	0.51 (0.33-0.77)	0.0003	0.37
Multivariable HR (95% CI)§	1 (ref)	1.04 (0.74-1.47)	0.90 (0.62-1.31)	0.92 (0.61-1.39)	0.59 (0.38-0.91)	0.01	0.34
High							
No. cases (n=274)	36	81	65	43	49		
Age-adjusted HR (95% CI)	1 (ref)	1.43 (0.96-2.13)	1.23 (0.81-1.86)	1.12 (0.72-1.76)	0.98 (0.63-1.52)	0.27	
Multivariable HR (95% CI)§	1 (ref)	1.47 (0.99-2.19)	1.28 (0.84-1.96)	1.22 (0.76-1.94)	1.16 (0.73-1.84)	0.80	
MSI-High							
CD45RO⁺							
Low							
No. cases (n=36)	10	6	8	5	7		
Age-adjusted HR (95% CI)	1 (ref)	0.36 (0.13-1.00)	0.57 (0.22-1.46)	0.44 (0.15-1.30)	0.49 (0.18-1.33)	0.34	
Multivariable HR (95% CI)§	1 (ref)	0.37 (0.13-1.03)	0.57 (0.22-1.48)	0.46 (0.15-1.39)	0.56 (0.21-1.52)	0.46	
High							
No. cases (n=77)	11	18	21	16	11		
Age-adjusted HR (95% CI)	1 (ref)	0.99 (0.47-2.11)	1.13 (0.54-2.36)	1.09 (0.50-2.37)	0.56 (0.24-1.31)	0.16	
Multivariable HR (95% CI)§	1 (ref)	1.01 (0.48-2.16)	1.17 (0.55-2.46)	1.20 (0.54-2.63)	0.67 (0.28-1.58)	0.37	

Microsatellite instability
Non-MSI-High

FOXP3⁺**Low**

No. cases (n=292)	51	77	78	52	34		
Age-adjusted HR (95% CI)	1 (ref)	0.94 (0.66-1.34)	1.03 (0.72-1.47)	0.92 (0.62-1.36)	0.46 (0.30-0.71)	0.0005	0.19
Multivariable HR (95% CI)§	1 (ref)	0.97 (0.67-1.39)	1.09 (0.75-1.57)	1.00 (0.66-1.51)	0.55 (0.34-0.87)	0.02	0.19

High

No. cases (n=261)	36	81	51	41	52		
Age-adjusted HR (95% CI)	1 (ref)	1.39 (0.93-2.06)	0.91 (0.59-1.41)	1.05 (0.66-1.65)	1.00 (0.65-1.54)	0.35	
Multivariable HR (95% CI)§	1 (ref)	1.42 (0.95-2.12)	0.95 (0.61-1.48)	1.13 (0.71-1.81)	1.19 (0.75-1.88)	0.91	

MSI-High**FOXP3⁺****Low**

No. cases (n=38)	9	11	10	2	6		
Age-adjusted HR (95% CI)	1 (ref)	0.79 (0.32-1.92)	0.73 (0.29-1.82)	0.19 (0.04-0.87)	0.45 (0.16-1.30)	0.05	
Multivariable HR (95% CI)§	1 (ref)	0.80 (0.33-1.96)	0.73 (0.29-1.83)	0.20 (0.04-0.96)	0.54 (0.19-1.58)	0.10	

High

No. cases (n=67)	9	12	19	17	10		
Age-adjusted HR (95% CI)	1 (ref)	0.79 (0.33-1.88)	1.25 (0.56-2.78)	1.40 (0.62-3.16)	0.60 (0.24-1.50)	0.50	
Multivariable HR (95% CI)§	1 (ref)	0.81 (0.34-1.94)	1.29 (0.58-2.89)	1.51 (0.66-3.46)	0.72 (0.29-1.82)	0.82	

CI, confidence interval; HR, hazard ratio.

Duplication-method Cox proportional cause-specific hazards regression for competing risks data was used to compute HRs and 95% CIs.

All analyses were stratified by age (in month), year of questionnaire return and sex.

*: Linear trend test using the median intake of each category.

¶: The likelihood ratio test was used to test for the heterogeneity of the association between total calcium intake and colorectal cancer risk by densities of tumor-infiltrating T-cell subsets.

§: Multivariable hazard ratios were adjusted for **age** (in month), **race** (Caucasian vs. non-Caucasian), **adult BMI** (< 25, 25 -< 27.5, 27.5 -< 30, or ≥ 30 kg/m²), **smoking** (0, 1-10, or > 10 pack-years), **history of colorectal cancer in a parent or sibling** (yes or no), **history of sigmoidoscopy/colonoscopy** (yes or no), **physical activity** (< 3, 3-< 27, ≥ 27 MET-hrs/wk), **regular aspirin use** (yes, no), **alcohol consumption** (0 -< 5, 5 -< 15, or ≥ 15 g/d), energy-adjusted total intake of **folate**, **vitamin D**, **red meat** and **processed meat** (all in tertiles).

Supplementary Table 6. Total calcium intake and 8-year lag colorectal cancer risk according to densities of tumor-infiltrating T-cell subsets in the Nurses' Health Study (1980-2012) and the Health Professionals Follow-up Study (1986-2012)

	Total calcium intake (mg/d)					P _{trend} *	P _{heterogeneity} †
	<600	600-799	800-999	1000-1199	≥1200		
CD3⁺							
Low							
No. cases (n=202)	56	45	28	32	41		
Age-adjusted HR (95% CI)	1 (ref)	0.72 (0.46-1.14)	0.64 (0.37-1.09)	0.97 (0.59-1.61)	0.58 (0.36-0.94)	0.07	0.77
Multivariable HR (95% CI)§	1 (ref)	0.75 (0.48-1.19)	0.68 (0.40-1.18)	1.07 (0.65-1.78)	0.68 (0.41-1.10)	0.26	0.81
High							
No. cases (n=230)	62	55	40	24	49		
Age-adjusted HR (95% CI)	1 (ref)	0.74 (0.46-1.18)	0.94 (0.58-1.53)	0.67 (0.38-1.18)	0.68 (0.44-1.07)	0.14	
Multivariable HR (95% CI)§	1 (ref)	0.77 (0.48-1.24)	1.01 (0.62-1.64)	0.74 (0.42-1.31)	0.78 (0.50-1.24)	0.40	
CD8⁺							
Low							
No. cases (n=224)	59	51	31	33	50		
Age-adjusted HR (95%CI)	1 (ref)	0.77 (0.50-1.19)	0.65 (0.39-1.08)	0.79 (0.48-1.31)	0.62 (0.40-0.96)	0.06	0.95
Multivariable HR (95% CI)§	1 (ref)	0.80 (0.52-1.24)	0.69 (0.41-1.15)	0.87 (0.53-1.45)	0.71 (0.46-1.11)	0.22	0.91
High							
No. cases (n=208)	61	49	38	21	39		
Age-adjusted HR (95%CI)	1 (ref)	0.71 (0.44-1.16)	1.02 (0.63-1.68)	0.78 (0.44-1.38)	0.60 (0.37-0.99)	0.07	
Multivariable HR (95% CI)§	1 (ref)	0.73 (0.45-1.20)	1.09 (0.66-1.79)	0.85 (0.48-1.50)	0.68 (0.41-1.13)	0.21	
CD45RO⁺							
Low							
No. cases (n=219)	66	47	32	34	40		
Age-adjusted HR (95%CI)	1 (ref)	0.56 (0.35-0.91)	0.63 (0.37-1.08)	0.89 (0.54-1.47)	0.49 (0.30-0.79)	0.03	0.35
Multivariable HR (95% CI)§	1 (ref)	0.58 (0.36-0.95)	0.67 (0.39-1.15)	0.98 (0.59-1.62)	0.56 (0.34-0.91)	0.11	0.36
High							
No. cases (n=222)	55	53	39	23	52		
Age-adjusted HR (95%CI)	1 (ref)	0.94 (0.60-1.47)	1.01 (0.63-1.63)	0.76 (0.44-1.32)	0.80 (0.52-1.25)	0.27	
Multivariable HR (95% CI)§	1 (ref)	0.97 (0.62-1.52)	1.08 (0.66-1.75)	0.83 (0.47-1.45)	0.91 (0.58-1.42)	0.61	
FOXP3⁺							
Low							
No. cases (n=201)	62	47	34	21	37		
Age-adjusted HR (95%CI)	1 (ref)	0.65 (0.41-1.03)	0.73 (0.45-1.21)	0.61 (0.34-1.09)	0.60 (0.38-0.95)	0.07	0.56
Multivariable HR (95% CI)§	1 (ref)	0.67 (0.42-1.06)	0.78 (0.47-1.30)	0.67 (0.37-1.20)	0.68 (0.42-1.10)	0.21	0.57

High						
No. cases (n=228)	52	51	38	34	53	
Age-adjusted HR (95%CI)	1 (ref)	0.90 (0.56-1.42)	0.97 (0.58-1.60)	1.10 (0.67-1.82)	0.75 (0.47-1.18)	0.25
Multivariable HR (95% CI)§	1 (ref)	0.93 (0.58-1.48)	1.03 (0.62-1.71)	1.20 (0.72-1.99)	0.85 (0.53-1.36)	0.58

CI, confidence interval; HR, hazard ratio.

Duplication-method Cox proportional cause-specific hazards regression for competing risks data was used to compute HRs and 95% CIs.

All analyses were stratified by age (in month) and year of questionnaire return.

*: Linear trend test using the median intake of each category.

¶: The likelihood ratio test was used to test for the heterogeneity of the association between total calcium intake and colorectal cancer risk by densities of tumor-infiltrating T-cell subsets.

§: Multivariable hazard ratios were adjusted for **age** (in month), **race** (Caucasian vs. non-Caucasian), **adult BMI** (< 25, 25 -< 27.5, 27.5 -< 30, or ≥ 30 kg/m²), **smoking** (0, 1-10, or > 10 pack-years), **history of colorectal cancer in a parent or sibling** (yes or no), **history of sigmoidoscopy/colonoscopy** (yes or no), **physical activity** (< 3, 3-< 27, ≥ 27 MET-hrs/wk), **regular aspirin use** (yes, no), **alcohol consumption** (0 -< 5, 5 -< 15, or ≥ 15 g/d), energy-adjusted total intake of **folate**, **vitamin D**, **red meat** and **processed meat** (all in tertiles).

Supplementary Table 7. Total calcium intake and risk of colorectal cancer according to tumor CASR expression and densities of tumor-infiltrating T-cell subsets in the Nurses' Health Study (1980-2012) and Health Professionals Follow-up Study (1986-2012)

	Total calcium intake (mg/d)					<i>p</i> _{trend} *
	<600	600-799	800-999	1000-1199	≥1200	
CASR expression status						
Negative						
CD3⁺						
Low						
Age-adjusted HR (95% CI)	1 (ref)	0.69 (0.30-1.59)	0.57 (0.23-1.40)	0.25 (0.07-0.90)	0.61 (0.25-1.51)	0.18
Multivariable HR (95% CI)§	1 (ref)	0.68 (0.29-1.55)	0.55 (0.22-1.37)	0.25 (0.07-0.92)	0.65 (0.26-1.63)	0.23
High						
Age-adjusted HR (95% CI)	1 (ref)	0.92 (0.35-2.38)	1.02 (0.39-2.62)	0.86 (0.31-2.42)	0.73 (0.37-2.00)	0.50
Multivariable HR (95% CI)§	1 (ref)	0.92 (0.35-2.41)	1.00 (0.39-2.59)	0.88 (0.31-2.50)	0.80 (0.29-2.21)	0.63
Positive						
CD3⁺						
Low						
Age-adjusted HR (95% CI)	1 (ref)	1.03 (0.69-1.53)	0.72 (0.47-1.12)	0.96 (0.62-1.49)	0.58 (0.36-0.92)	0.01
Multivariable HR (95% CI)§	1 (ref)	1.01 (0.68-1.52)	0.71 (0.46-1.12)	0.95 (0.60-1.51)	0.62 (0.37-1.01)	0.04
High						
Age-adjusted HR (95% CI)	1 (ref)	1.41 (0.91-2.19)	1.43 (0.92-2.22)	1.14 (0.70-1.86)	0.80 (0.48-1.32)	0.06
Multivariable HR (95% CI)§	1 (ref)	1.42 (0.91-2.21)	1.42 (0.90-2.24)	1.17 (0.70-1.95)	0.87 (0.52-1.48)	0.18
CASR expression status						
Negative						
CD8⁺						
Low						
Age-adjusted HR (95% CI)	1 (ref)	0.73 (0.30-1.79)	0.95 (0.41-2.24)	0.27 (0.07-0.99)	0.65 (0.26-1.63)	0.24
Multivariable HR (95% CI)§	1 (ref)	0.72 (0.29-1.74)	0.93 (0.39-2.20)	0.26 (0.07-0.99)	0.70 (0.27-1.79)	0.32
High						
Age-adjusted HR (95% CI)	1 (ref)	0.85 (0.34-2.13)	0.59 (0.21-1.67)	0.91 (0.33-2.46)	0.83 (0.31-2.22)	0.83
Multivariable HR (95% CI)§	1 (ref)	0.84 (0.33-2.12)	0.56 (0.20-1.60)	0.90 (0.33-2.48)	0.88 (0.32-2.38)	0.91
Positive						
CD8⁺						
Low						
Age-adjusted HR (95% CI)	1 (ref)	1.03 (0.68-1.57)	0.98 (0.64-1.51)	0.93 (0.58-1.48)	0.56 (0.34-0.92)	0.01
Multivariable HR (95% CI)§	1 (ref)	1.02 (0.66-1.56)	0.95 (0.61-1.48)	0.92 (0.57-1.50)	0.60 (0.36-1.01)	0.03

High							
Age-adjusted HR (95% CI)	1 (ref)	1.44 (0.94-2.20)	1.22 (0.79-1.90)	1.16 (0.72-1.87)	0.82 (0.50-1.33)	0.08	
Multivariable HR (95% CI)§	1 (ref)	1.43 (0.94-2.20)	1.21 (0.77-1.90)	1.16 (0.71-1.92)	0.88 (0.52-1.47)	0.17	
CASR expression status							
Negative							
CD45RO⁺							
Low							
Age-adjusted HR (95% CI)	1 (ref)	0.95 (0.33-2.69)	1.35 (0.49-3.72)	0.45 (0.11-1.84)	0.85 (0.28-2.59)	0.53	
Multivariable HR (95% CI)§	1 (ref)	0.92 (0.32-2.60)	1.33 (0.48-3.66)	0.47 (0.11-1.91)	0.91 (0.30-2.82)	0.65	
High							
Age-adjusted HR (95% CI)	1 (ref)	0.58 (0.27-1.26)	0.49 (0.22-1.12)	0.53 (0.23-1.27)	0.51 (0.22-1.17)	0.19	
Multivariable HR (95% CI)§	1 (ref)	0.58 (0.27-1.27)	0.48 (0.21-1.10)	0.54 (0.23-1.31)	0.56 (0.24-1.29)	0.26	
Positive							
CD45RO⁺							
Low							
Age-adjusted HR (95% CI)	1 (ref)	0.90 (0.61-1.33)	0.80 (0.53-1.19)	0.84 (0.55-1.29)	0.54 (0.34-0.85)	0.006	
Multivariable HR (95% CI)§	1 (ref)	0.90 (0.61-1.33)	0.79 (0.52-1.20)	0.85 (0.54-1.34)	0.58 (0.36-0.94)	0.02	
High							
Age-adjusted HR (95% CI)	1 (ref)	1.84 (1.14-2.96)	1.65 (1.01-2.69)	1.49 (0.88-2.52)	1.10 (0.65-1.87)	0.34	
Multivariable HR (95% CI)§	1 (ref)	1.82 (1.13-2.95)	1.64 (0.99-2.71)	1.54 (0.89-2.64)	1.22 (0.70-2.12)	0.67	
CASR expression status							
Negative							
FOXP3⁺							
Low							
Age-adjusted HR (95% CI)	1 (ref)	1.93 (0.62-6.07)	1.88 (0.58-6.06)	0.89 (0.22-3.63)	1.19 (0.34-4.19)	0.55	
Multivariable HR (95% CI)§	1 (ref)	1.87 (0.59-5.87)	1.79 (0.56-5.80)	0.90 (0.22-3.68)	1.31 (0.37-4.63)	0.70	
High							
Age-adjusted HR (95% CI)	1 (ref)	0.46 (0.20-1.05)	0.49 (0.21-1.12)	0.37 (0.14-0.98)	0.54 (0.24-1.24)	0.25	
Multivariable HR (95% CI)§	1 (ref)	0.46 (0.20-1.05)	0.47 (0.20-1.08)	0.37 (0.14-0.98)	0.58 (0.25-1.34)	0.31	
Positive							
FOXP3⁺							
Low							
Age-adjusted HR (95% CI)	1 (ref)	0.95 (0.64-1.41)	0.97 (0.65-1.45)	0.90 (0.58-1.39)	0.48 (0.30-0.78)	0.002	
Multivariable HR (95% CI)§	1 (ref)	0.95 (0.63-1.41)	0.96 (0.63-1.45)	0.90 (0.57-1.43)	0.53 (0.32-0.88)	0.01	
High							
Age-adjusted HR (95% CI)	1 (ref)	1.63 (1.00-2.64)	1.31 (0.79-2.16)	1.41 (0.83-2.38)	1.10 (0.65-1.87)	0.56	

Multivariable HR (95% CI)§ 1 (ref) 1.61 (0.98-2.62) 1.27 (0.76-2.13) 1.40 (0.81-2.42) 1.21 (0.69-2.11) 0.86

CI, confidence interval; HR, hazard ratio.

Duplication-method Cox proportional cause-specific hazards regression for competing risks data was used to compute HRs and 95% CIs.

All analyses were stratified by age (in month), year of questionnaire return and sex.

*: Linear trend test using the median intake of each category.

§: Multivariable hazard ratios were adjusted for **age** (in month), **race** (Caucasian vs. non-Caucasian), **adult BMI** (< 25, 25 -< 27.5, 27.5 -< 30, or ≥ 30 kg/m²), smoking (0, 1-10, or > 10 pack-years), **history of colorectal cancer in a parent or sibling** (yes or no), **history of sigmoidoscopy/colonoscopy** (yes or no), **physical activity** (< 3, 3-< 27, ≥ 27 MET-hrs/wk), **regular aspirin use** (yes, no), **alcohol consumption** (0 -< 5, 5 -< 15, or ≥ 15 g/d), energy-adjusted total intake of **folate**, **vitamin D**, **red meat** and **processed meat** (all in tertiles).