436 2009;**89**:1418–24.

437 27. Wu K, Giovannucci E, Byrne C, Platz EA, Fuchs C, Willett WC, Sinha R. Meat mutagens

438 and risk of distal colon adenoma in a cohort of U.S. men. *Cancer Epidemiol Biomarkers Prev*

439 2006;**15**:1120–5.

440 28. MacLean CH, Newberry SJ, Mojica WA, Khanna P, Issa AM, Suttorp MJ, Lim YW,

441 Traina SB, Hilton L, Garland R, Morton SC. Effects of omega-3 fatty acids on cancer risk: a

442 systematic review. *JAMA* 2006;**295**:403–15.

443 29. Zock PL, Katan MB. Linoleic acid intake and cancer risk: a review and meta-analysis. *Am*

444 *J Clin Nutr* 1998;**68**:142–53.

445 30. Gago-Dominguez M, Yuan JM, Sun CL, Lee HP, Yu MC. Opposing effects of dietary n-3

446 and n-6 fatty acids on mammary carcinogenesis: The Singapore Chinese Health Study. *Br J*

447 *Cancer* 2003;**89**:1686–92.

448 31. Sonestedt E, Ericson U, Gullberg B, Skog K, Olsson H, Wirfält E. Do both heterocyclic

449 amines and omega-6 polyunsaturated fatty acids contribute to the incidence of breast cancer in

450 postmenopausal women of the Malmö diet and cancer cohort? *Int J Cancer*

451 2008;**123**:1637–43.

452 32. Elmadfa I, Kornsteiner M. Dietary fat intake—a global perspective. *Ann Nutr Metab*

453 2009;**54** Suppl 1:8–14.

454 33. Kobayashi M, Sasaki S, Hamada GS, Tsugane S. Serum n-3 fatty acids, fish consumption

455 and cancer mortality in six Japanese populations in Japan and Brazil. *Jpn J Cancer Res*

456 1999;**90**:914–21.

Table 1. Baseline characteristics of study subjects according to marine n-3, total n-3, and total n-6 poly unsaturated fatty acid (PUFA) intake: the JPHC Study (1995)

	Marine n-3 PUFA*			Total n-3 PUFA†			Total n-6 PUFA		
	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5
Men									
Marine n-3 PUFA (g/d)	0.5	1.1	2.5	0.6	1.1	2.3	1.0	1.3	1.3
Total n-3 PUFA (g/d)	2.1	2.8	4.6	1.7	2.9	4.8	2.1	3.1	3.9
Total n-6 PUFA (g/d)	8.4	8.8	9.3	6.4	9.0	10.7	5.6	8.6	12.6
Age	56.0	56.6	58.3	55.6	56.7	58.5	56.2	56.5	57.9
Overweight (%)‡	30.9	27.8	26.8	28.0	28.4	28.2	26.3	28.4	31.6
Current smoker (%)	45.0	46.9	46.3	53.2	45.4	41.9	56.0	45.9	36.6
Regular drinker (%)§	71.6	65.3	63.5	78.5	66.6	57.1	82.8	67.4	49.8
METs‖ (METs-hour/d)	32.8	32.2	32.4	32.5	32.5	32.3	32.4	32.4	32.2
History of DM (%)**	5.3	7.1	8.9	5.3	6.6	10.2	5.8	6.7	9.6
CRC screening, yes (%)††	28.2	32.7	33.7	27.1	33.3	33.9	27.5	33.8	32.2
Dietary intake									
Total energy (kcal/d)	2330.3	2043.4	2287.9	2216.5	2109.1	2238.7	2158.6	2166.3	2174.5
Calcium (mg/d)	506.3	524.4	537.2	462.4	524.2	581.6	442.7	529.1	601.2
Vitamin D (μg/d)	4.2	9.1	18.3	5.1	9.2	17.1	8.0	10.6	10.7
Fiber (g/d)	10.4	11.6	12.4	8.4	11.6	14.2	8.2	11.6	14.4
Red meat (g/d)	55.6	53.9	51.2	38.8	58.0	59.1	31.4	52.9	78.2
Fish (g/d)	39.6	84.1	166.9	45.4	84.4	158.4	74.9	96.9	99.1
Vegetables (g/d)	175.9	193.5	210.6	115.4	195.2	267.8	122.9	191.2	266.0
Dressing (g/d)	1.1	1.2	1.2	0.5	1.2	1.7	0.4	1.1	2.1
Cook oil (g/d)	8.7	9.6	11.9	5.7	9.9	14.1	6.1	9.8	13.8
Fats and oils (g/d)	10.7	11.5	13.3	7.1	12.0	15.9	6.9	11.5	17.0
Women									
Marine n-3 PUFA (g/d)	0.4	1.0	2.1	0.5	1.0	2.0	1.0	1.2	1.0
Total n-3 PUFA (g/d)	2.4	3.1	4.5	2.0	3.1	4.7	2.6	3.3	3.8
Total n-6 PUFA (g/d)	9.2	9.0	9.1	7.4	9.2	10.3	6.3	8.9	12.3
Age	56.8	57.0	58.3	56.8	56.9	58.3	58.0	56.8	57.5
Overweight (%)‡	30.5	26.7	29.4	28.2	28.2	29.7	27.4	27.2	31.0
Current smoker (%)	5.8	5.6	4.9	7.1	5.6	4.6	7.5	5.1	4.9
Regular drinker (%)§	11.6	13.5	11.1	15.4	12.4	9.8	17.0	12.3	8.9
METs‖ (METs-hour/d)	31.6	31.6	31.6	31.3	31.7	31.6	31.2	31.7	31.5
History of DM (%)**	3.2	3.7	4.4	2.8	3.5	5.0	3.2	3.4	4.9
CRC screening, yes (%)††	28.1	30.9	33.0	26.4	30.8	33.4	27.9	32.1	30.7
Dietary intake									
Total energy (kcal/d)	1995.5	1752.8	1975.6	1898.6	1829.0	1909.1	1844.4	1872.4	1848.6
Calcium (mg/d)	585.4	575.2	563.9	573.0	565.5	600.6	576.8	565.4	604.6
Vitamin D (μg/d)	4.4	8.9	17.0	5.4	9.0	15.8	9.0	10.2	9.4
Fiber (g/d)	13.5	14.2	14.3	11.6	14.2	16.3	12.1	14.1	15.8
Red meat (g/d)	55.4	49.3	44.2	38.8	57.9	59.1	30.9	49.4	68.6
Fish (g/d)	40.9	83.5	158.8	47.9	84.7	149.6	83.7	94.0	89.2
Vegetables (g/d)	239.1	240.5	247.8	163.6	245.2	318.9	181.9	242.5	302.0
Dressing (g/d)	1.7	1.8	1.6	1.0	1.8	2.2	0.8	1.7	2.6
Cook oil (g/d)	10.6	10.7	12.3	7.3	11.1	14.7	7.8	11.1	14.3
Fats and oils (g/d)	12.9	12.5	13.5	9.0	13.0	16.2	8.6	12.7	17.2

Values are means unless otherwise specified.

icosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) + docosapentaenoic acid (DPA)

Marine PUFA+α-linolenic acid (ALA)

BMI 25<=

Alcohol drinking 1d/wk+

Metabolic equivalent tasks

Past history of or medication use for diabetes mellitus (DM)

Colorectal cancer (CRC) screening of fecal occult blood test or barium enema or colonoscopy

Table 2. Associations of n-3 and n-6 polyunsaturated fatty acids (PUFAs) and its ratio and colon and rectal cancer risk in men

PUFA (median g/d)	Person-year	Colon: All (n=521) Cases	RR† (95%CI)	Colon: Invasive* Proximal (n=142) Cases	RR† (95%CI)	Colon: Invasive* Distal (n=197) Cases	RR† (95%CI)	Rectum: All (n=253) Cases	RR† (95%CI)	Rectum: Invasive* (n=214) Cases	RR† (95%CI)
EPA‡											
Q1 (0.16)	76691	104	1.00	31	1.00	37	1.00	55	1.00	47	1.00
Q2 (0.27)	76031	99	0.89 (0.65-1.23)	35	0.86 (0.48-1.52)	37	1.13 (0.67-1.92)	44	0.76 (0.47-1.21)	38	0.76 (0.46-1.27)
Q3 (0.37)	75551	98	0.81 (0.56-1.19)	19	0.34 (0.16-0.72)	45	1.48 (0.81-2.69)	32	0.51 (0.28-0.92)	28	0.54 (0.28-1.02)
Q4 (0.50)	76514	108	0.79 (0.52-1.20)	32	0.39 (0.18-0.86)	38	1.34 (0.68-2.67)	49	0.74 (0.40-1.39)	42	0.78 (0.40-1.54)
Q5 (0.77)	75895	112	0.81 (0.50-1.30)	25	0.27 (0.11-0.66)	40	1.34 (0.68-2.67)	73	1.06 (0.53-2.11)	59	1.13 (0.53-2.38)
P for trend			*0.53*		*0.01*		*0.29*		*0.23*		*0.21*
DHA§											
Q1 (0.24)	76842	101	1.00	26	1.00	38	1.00	54	1.00	46	1.00
Q2 (0.41)	76020	104	0.97 (0.70-1.36)	36	1.18 (0.63-2.23)	38	1.06 (0.62-1.82)	44	0.86 (0.53-1.40)	40	0.91 (0.54-1.55)
Q3 (0.56)	75764	101	0.85 (0.57-1.27)	23	0.58 (0.26-1.29)	48	1.35 (0.72-2.54)	35	0.62 (0.34-1.16)	28	0.58 (0.29-1.15)
Q4 (0.74)	76389	93	0.76 (0.48-1.20)	27	0.49 (0.20-1.19)	29	1.03 (0.49-2.17)	51	0.89 (0.46-1.74)	45	0.94 (0.46-1.94)
Q5 (1.14)	75667	122	1.02 (0.61-1.70)	30	0.48 (0.18-1.29)	44	1.83 (0.80-4.17)	69	1.12 (0.53-2.36)	55	1.13 (0.50-2.54)
P for trend			*0.58*		*0.65*		*0.11*		*0.33*		*0.38*
DPA‖											
Q1 (0.07)	77545	103	1.00	29	1.00	35	1.00	54	1.00	46	1.00
Q2 (0.10)	76560	108	1.05 (0.77-1.44)	32	0.97 (0.53-1.75)	43	1.41 (0.84-2.37)	47	0.92 (0.58-1.46)	41	0.92 (0.56-1.51)
Q3 (0.13)	75697	98	0.87 (0.60-1.26)	27	0.66 (0.32-1.34)	47	1.49 (0.82-2.70)	31	0.60 (0.33-1.08)	26	0.59 (0.31-1.11)
Q4 (0.16)	75627	104	0.90 (0.59-1.37)	30	0.52 (0.23-1.16)	30	1.19 (0.59-2.41)	48	0.87 (0.46-1.65)	42	0.90 (0.45-1.79)
Q5 (0.23)	75253	108	0.86 (0.53-1.38)	24	0.35 (0.14-0.88)	42	1.80 (0.83-3.91)	73	1.34 (0.67-2.68)	59	1.37 (0.65-2.91)
P for trend			*0.47*		*0.02*		*0.19*		*0.14*		*0.15*
Marine n-3 PUFA**											
Q1 (0.49)	76696	101	1.00	28	1.00	38	1.00	57	1.00	49	1.00
Q2 (0.79)	76078	102	0.95 (0.68-1.34)	34	0.97 (0.51-1.83)	37	1.09 (0.63-1.89)	42	0.69 (0.42-1.13)	36	0.71 (0.42-1.21)
Q3 (1.06)	75722	99	0.85 (0.57-1.29)	22	0.48 (0.21-1.08)	47	1.47 (0.78-2.79)	32	0.51 (0.27-0.95)	27	0.50 (0.25-0.99)
Q4 (1.43)	76632	102	0.83 (0.52-1.31)	31	0.47 (0.20-1.15)	33	1.24 (0.59-2.59)	49	0.72 (0.36-1.41)	43	0.78 (0.37-1.61)
Q5 (2.18)	75555	117	0.96 (0.57-1.61)	27	0.35 (0.14-0.88)	42	1.82 (0.79-4.20)	73	1.07 (0.51-2.26)	59	1.14 (0.51-2.57)
P for trend			*0.82*		*0.05*		*0.16*		*0.15*		*0.14*
ALA††											
Q1 (1.21)	76304	109	1.00	32	1.00	30	1.00	52	1.00	46	1.00
Q2 (1.61)	76159	115	1.07 (0.80-1.43)	34	0.99 (0.58-1.69)	45	1.64 (0.99-2.72)	54	1.07 (0.70-1.65)	46	1.00 (0.63-1.58)
Q3 (1.91)	76126	100	0.92 (0.66-1.28)	27	0.74 (0.40-1.37)	36	1.25 (0.70-2.24)	45	0.91 (0.56-1.49)	36	0.75 (0.44-1.28)
Q4 (2.23)	76065	99	0.92 (0.64-1.33)	23	0.62 (0.31-1.26)	46	1.66 (0.90-3.05)	49	0.98 (0.58-1.67)	39	0.79 (0.45-1.41)
Q5 (2.76)	76029	98	0.84 (0.56-1.28)	26	0.61 (0.27-1.34)	40	1.31 (0.65-2.63)	53	1.10 (0.61-1.98)	47	0.92 (0.49-1.74)
P for trend			*0.31*		*0.14*		*0.70*		*0.80*		*0.77*
Total n-3¶											
Q1 (1.79)	76334	112	1.00	33	1.00	37	1.00	54	1.00	47	1.00
Q2 (2.42)	76306	100	0.87 (0.64-1.17)	30	0.75 (0.43-1.32)	37	0.98 (0.59-1.63)	45	0.93 (0.59-1.46)	38	0.83 (0.51-1.35)
Q3 (2.90)	76444	103	0.85 (0.61-1.20)	26	0.56 (0.29-1.08)	45	1.21 (0.70-2.09)	38	0.76 (0.45-1.30)	33	0.67 (0.38-1.18)
Q4 (3.47)	76406	98	0.74 (0.50-1.09)	26	0.46 (0.22-0.97)	38	0.95 (0.51-1.79)	47	0.94 (0.53-1.67)	39	0.79 (0.43-1.48)
Q5 (4.48)	75193	108	0.76 (0.48-1.18)	27	0.42 (0.18-0.98)	40	1.07 (0.52-2.20)	69	1.33 (0.70-2.51)	57	1.13 (0.57-2.24)
P for trend			*0.24*		*0.05*		*0.92*		*0.18*		*0.40*
Total n-6											
Q1 (5.85)	75231	114	1.00	32	1.00	33	1.00	56	1.00	49	1.00
Q2 (7.43)	76699	120	1.08 (0.82-1.44)	37	1.06 (0.63-1.78)	40	1.40 (0.85-2.30)	53	0.92 (0.61-1.40)	46	0.90 (0.58-1.41)
Q3 (8.60)	76712	95	0.91 (0.66-1.25)	23	0.65 (0.35-1.22)	36	1.25 (0.72-2.18)	50	0.88 (0.55-1.38)	38	0.71 (0.42-1.17)
Q4 (9.85)	76146	104	1.04 (0.74-1.46)	31	0.83 (0.44-1.58)	44	1.71 (0.97-3.03)	48	0.85 (0.52-1.41)	40	0.74 (0.43-1.26)
Q5 (11.97)	75893	88	0.85 (0.57-1.25)	19	0.46 (0.21-0.99)	44	1.59 (0.85-2.99)	46	0.86 (0.50-1.50)	41	0.77 (0.43-1.40)
P for trend			*0.35*		*0.04*		*0.17*		*0.61*		*0.38*
n-3/n-6											
Q1 (0.23)	75806	91	1.00	30	1.00	43	1.00	45	1.00	39	1.00
Q2 (0.28)	76584	92	1.02 (0.75-1.40)	16	0.58 (0.34-1.11)	41	0.97 (0.61-1.55)	42	1.01 (0.64-1.61)	36	1.02 (0.62-1.68)
Q3 (0.32)	76713	108	1.18 (0.85-1.65)	34	1.19 (0.65-2.19)	33	0.80 (0.47-1.37)	44	1.02 (0.61-1.69)	37	0.97 (0.56-1.68)
Q4 (0.37)	76595	106	1.10 (0.76-1.59)	31	0.99 (0.49-1.97)	33	0.83 (0.46-1.49)	51	1.23 (0.72-2.12)	46	1.29 (0.73-2.31)
Q5 (0.48)	7E+05	124	1.22 (0.81-1.85)	31	0.92 (0.42-2.01)	47	1.23 (0.65-2.34)	71	1.62 (0.89-2.93)	56	1.56 (0.82-2.97)
P for trend			*0.35*		*0.96*		*0.39*		*0.05*		*0.10*

* Cases restricted to invasive (tumor over the mucosal layer) cancer.
† Adjusted for age, area, BMI, smoking status, alcohol drinking, past history of or medication use for DM, METs, screening for CRC, total calorie, intal calcium, vitamin D, fiber, and red meat
‡ eicosapentaenoic acid
§ docosahexaenoic acid
‖ docosapentaenoic acid
** EPA + DHA + DPA
†† α-linolenic acid
¶ Marine n-3 PUFA + ALA

Table 3. Associations of n-3 and n-6 polyunsaturate fatty acids (PUFAs) and its ratio and colon and rectal cancer risk in women

PUFA (median g/d)	Person-year	Colon: All (n=350) Cases	RR† (95%CI)	Colon: Invasive* Proximal (n=171) Cases	RR† (95%CI)	Colon: Invasive* Distal (n=88) Cases	RR† (95%CI)	Rectum: All (n=144) Cases	RR† (95%CI)	Rectum: Invasive* (n=126) Cases	RR† (95%CI)
EPA‡											
Q1 (0.16)	88555	62	1.00	31	1.00	14	1.00	28	1.00	27	1.00
Q2 (0.28)	88548	53	0.66 (0.42-1.04)	33	0.68 (0.36-1.26)	11	0.77 (0.31-1.93)	23	0.66 (0.35-1.26)	21	0.63 (0.33-1.24)
Q3 (0.37)	88849	80	0.91 (0.56-1.47)	40	0.82 (0.42-1.62)	20	1.02 (0.38-2.76)	27	0.71 (0.34-1.47)	24	0.68 (0.32-1.46)
Q4 (0.49)	90060	88	0.76 (0.44-1.30)	33	0.51 (0.23-1.09)	26	1.23 (0.42-3.59)	35	0.91 (0.41-2.03)	26	0.81 (0.34-1.93)
Q5 (0.73)	91140	67	0.49 (0.27-0.89)	34	0.45 (0.20-1.05)	17	0.57 (0.17-1.91)	31	0.74 (0.30-1.82)	28	0.78 (0.30-2.03)
P for trend			*0.01*		*0.07*		*0.22*		*0.68*		*0.83*
DHA§											
Q1 (0.26)	88654	61	1.00	31	1.00	13	1.00	26	1.00	26	1.00
Q2 (0.43)	88617	66	0.77 (0.50-1.19)	42	0.95 (0.52-1.75)	14	0.94 (0.37-2.39)	21	0.63 (0.32-1.22)	18	0.59 (0.29-1.22)
Q3 (0.57)	89078	66	0.83 (0.52-1.35)	29	0.51 (0.25-1.07)	19	1.14 (0.40-3.27)	30	0.84 (0.41-1.74)	27	1.14 (0.53-2.47)
Q4 (0.75)	89864	86	0.74 (0.44-1.26)	32	0.46 (0.21-1.03)	25	1.36 (0.44-4.23)	32	1.22 (0.55-2.71)	25	1.15 (0.46-2.86)
Q5 (1.10)	90938	71	0.50 (0.28-0.90)	37	0.47 (0.20-1.14)	17	0.62 (0.17-2.22)	35	1.14 (0.46-2.81)	30	1.36 (0.49-3.77)
P for trend			*0.01*		*0.13*		*0.21*		*0.57*		*0.38*
DPA‖											
Q1 (0.07)	89579	62	1.00	33	1.00	14	1.00	28	1.00	26	1.00
Q2 (0.10)	88874	61	0.85 (0.55-1.32)	36	0.73 (0.41-1.31)	11	0.69 (0.27-1.77)	21	0.70 (0.35-1.40)	20	0.65 (0.33-1.30)
Q3 (0.12)	88842	76	0.71 (0.43-1.20)	35	0.61 (0.31-1.20)	19	1.03 (0.39-2.72)	27	1.21 (0.57-2.54)	25	0.88 (0.41-1.87)
Q4 (0.15)	89281	84	0.76 (0.43-1.33)	35	0.48 (0.23-1.02)	25	1.29 (0.44-3.69)	35	1.28 (0.54-3.04)	25	1.10 (0.46-2.60)
Q5 (0.21)	90575	67	0.53 (0.29-1.00)	32	0.37 (0.16-0.85)	19	0.74 (0.23-2.42)	33	1.49 (0.57-3.87)	30	1.25 (0.48-3.29)
P for trend			*0.04*		*0.02*		*0.51*		*0.29*		*0.46*
Marine n-3 PUFA**											
Q1 (0.42)	76696	57	1.00	28	1.00	13	1.00	24	1.00	24	1.00
Q2 (0.71)	76078	42	0.93 (0.59-1.48)	38	1.04 (0.54-1.97)	15	1.05 (0.42-2.66)	25	0.97 (0.49-1.94)	22	0.86 (0.42-1.76)
Q3 (0.96)	75722	32	0.93 (0.55-1.58)	36	0.83 (0.40-1.76)	18	1.07 (0.36-3.16)	28	1.27 (0.58-2.79)	25	1.22 (0.54-2.76)
Q4 (1.28)	76632	49	0.88 (0.49-1.56)	33	0.61 (0.27-1.41)	25	1.35 (0.43-4.30)	33	1.60 (0.66-3.85)	26	1.48 (0.59-3.76)
Q5 (1.92)	75555	73	0.60 (0.31-1.14)	36	0.59 (0.24-1.45)	17	0.61 (0.17-2.24)	34	1.62 (0.61-4.32)	29	1.51 (0.53-4.28)
P for trend			*0.04*		*0.19*		*0.19*		*0.33*		*0.40*
ALA††											
Q1 (1.35)	76696	68	1.00	33	1.00	19	1.00	25	1.00	25	1.00
Q2 (1.68)	76078	66	0.94 (0.65-1.37)	27	0.79 (0.46-1.38)	19	1.02 (0.51-2.05)	34	1.28 (0.73-2.25)	26	0.98 (0.54-1.79)
Q3 (1.92)	75722	54	0.73 (0.49-1.10)	28	0.73 (0.41-1.29)	13	0.67 (0.30-1.51)	25	0.89 (0.47-1.68)	22	0.76 (0.39-1.48)
Q4 (2.18)	76632	82	1.05 (0.71-1.57)	45	1.11 (0.63-1.94)	17	0.72 (0.31-1.66)	28	1.04 (0.55-1.99)	26	0.96 (0.49-1.86)
Q5 (2.64)	75555	80	1.01 (0.65-1.57)	38	0.84 (0.45-1.59)	20	0.92 (0.38-2.22)	32	1.02 (0.50-2.06)	27	0.87 (0.41-1.82)
P for trend			*0.69*		*0.98*		*0.75*		*0.84*		*0.74*
Total n-3¶											
Q1 (2.13)	87986	63	1.00	32	1.00	15	1.00	22	1.00	21	1.00
Q2 (2.69)	89077	60	0.84 (0.56-1.25)	27	0.62 (0.35-1.10)	18	1.43 (0.64-3.17)	26	1.01 (0.54-1.91)	25	1.04 (0.54-2.00)
Q3 (3.11)	89126	71	0.87 (0.57-1.33)	39	0.75 (0.42-1.34)	11	0.87 (0.34-2.23)	31	1.37 (0.72-2.62)	26	1.31 (0.66-2.58)
Q4 (3.60)	90443	80	0.84 (0.53-1.31)	38	0.63 (0.34-1.19)	24	1.50 (0.60-3.75)	32	1.38 (0.69-2.78)	25	1.22 (0.58-2.57)
Q5 (4.48)	90520	76	0.68 (0.41-1.12)	35	0.55 (0.27-1.11)	20	0.81 (0.28-2.33)	33	1.13 (0.51-2.49)	29	1.16 (0.51-2.67)
P for trend			*0.15*		*0.16*		*0.54*		*0.78*		*0.76*
Total n-6											
Q1 (6.56)	87433	74	1.00	34	1.00	24	1.00	28	1.00	27	1.00
Q2 (7.89)	89676	53	0.71 (0.43-1.03)	28	0.74 (0.43-1.27)	9	0.35 (0.15-0.81)	24	0.75 (0.42-1.37)	21	0.70 (0.38-1.30)
Q3 (8.85)	89803	66	0.83 (0.57-1.21)	31	0.73 (0.42-1.27)	19	0.71 (0.35-1.44)	37	1.26 (0.72-2.19)	31	1.06 (0.59-1.90)
Q4 (9.90)	89917	92	1.12 (0.77-1.63)	48	1.13 (0.67-1.92)	18	0.66 (0.31-1.40)	29	0.91 (0.49-1.68)	26	0.82 (0.43-1.55)
Q5 (11.72)	90322	65	0.87 (0.57-1.31)	30	0.74 (0.40-1.35)	18	0.70 (0.32-1.57)	26	0.81 (0.42-1.56)	21	0.65 (0.32-1.32)
P for trend			*0.81*		*0.75*		*0.74*		*0.63*		*0.32*
n-3/ n-6											
Q1 (0.24)	88380	55	1.00	26	1.00	14	1.00	22	1.00	22	1.00
Q2 (0.29)	89276	59	1.11 (0.73-1.71)	28	0.94 (0.51-1.74)	13	1.34 (0.55-3.23)	28	1.24 (0.67-2.32)	27	1.26 (0.67-2.36)
Q3 (0.33)	89504	74	1.29 (0.82-2.02)	38	1.25 (0.66-2.36)	18	1.71 (0.68-4.32)	32	1.32 (0.67-2.58)	24	1.08 (0.53-2.21)
Q4 (0.38)	90334	89	1.33 (0.82-2.14)	46	1.41 (0.72-2.76)	24	1.89 (0.71-5.06)	35	1.54 (0.75-3.16)	27	1.41 (0.66-3.00)
Q5 (0.47)	89658	73	1.05 (0.61-1.79)	33	1.07 (0.50-2.30)	19	1.20 (0.40-3.62)	27	1.00 (0.44-2.27)	26	1.14 (0.48-2.70)
P for trend			*0.87*		*0.83*		*0.96*		*0.81*		*0.85*

* Cases restricted to invasive (tumor over the mucosal layer) cancer.

† Adjusted for age, area, BMI, smoking status, alcohol drinking, past history of or medication use of DM, METs, screening for CRC, total calorie intake of calcium, vitamin D, fiber, and red meat

‡ eicosapentaenoic acid

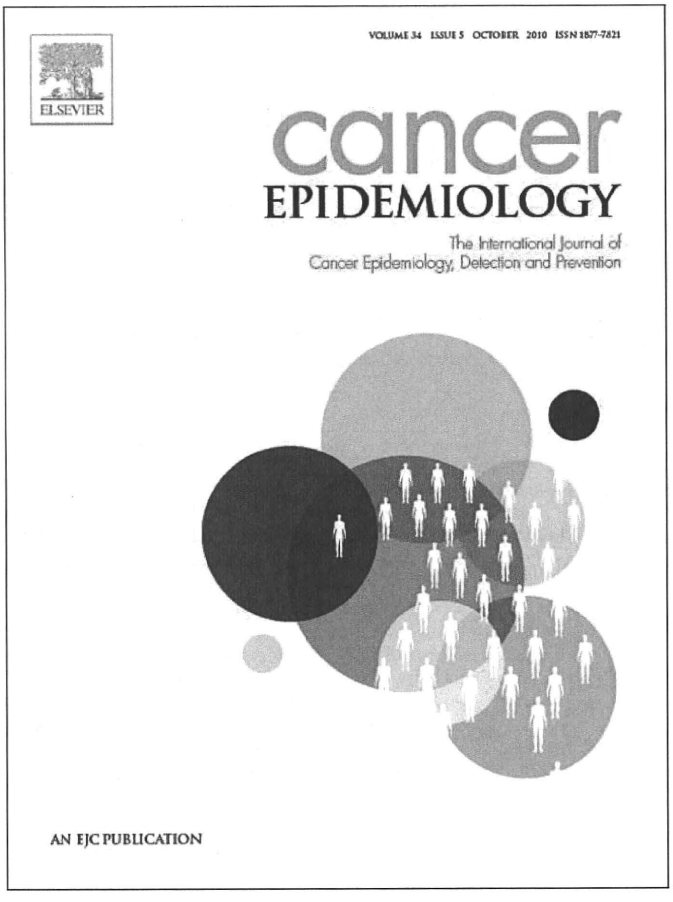
§ docosahexaenoic acid

‖ docosapentaenoic acid

** EPA + DHA + DPA

†† α - linolenic acid

¶ Marine n-3 PUFA + ALA



Cancer Epidemiology 34 (2010) 534–541

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

10-Year risk of colorectal cancer: Development and validation of a prediction model in middle-aged Japanese men

Enbo Ma, Shizuka Sasazuki *, Motoki Iwasaki, Norie Sawada, Manami Inoue

Shoichiro Tsugane for the Japan Public Health Center-based Prospective Study Group

Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

ARTICLE INFO

Article history:
Accepted 30 April 2010
Available online 31 May 2010

Keywords:
Prospective study
Epidemiologic method
Risk prediction
Colorectal cancer
Validation
Japanese men

ABSTRACT

Background: To estimate an individual's probability of developing colorectal cancer (CRC) may aid health professionals and individuals in improving lifestyle behaviors or deciding the screening regimens. As fewer studies on cancer risk prediction were seen so far, we initially developed an assessment tool with synthesizing key information from a variety of CRC risk factors through a large population-based cohort study. *Method:* The prediction model was derived from 28,115 men in the Japan Public Health Center-based (JPHC) Prospective Study Cohort II (follow-up: 1993–2005), with risk factors selected by Cox proportion hazard regression. 18,256 men in the JPHC Study Cohort I (follow-up: 1995–2005) were used to evaluate the model's performance. *Results:* 543 and 398 CRCs were diagnosed during the follow-up period in Cohorts II and I, respectively. The prediction model, including age, BMI, alcohol consumption, smoking status, and the daily physical activity level, showed modest discrimination ability for CRC ($C = 0.70$; 95% confidential interval, 0.68–0.72) in Cohort II and well calibrated in Cohort I (Hosmer–Lemeshow $\chi^2 = 14.2$, $P = 0.08$). *Conclusion:* The 10-year CRC risk prediction model may be used to estimate CRC risk in Japanese men. It may also play a role in the promotion of CRC prevention strategies.

1. Introduction

Colorectal cancer (CRC) was the second most commonly diagnosed cancer in the Japanese population in 2002 [1,2]. Approximately 11% of total cancer deaths in men and 14% in women were from CRCs in 2005 [2]. The high morbidity and mortality noted in the Japanese population were similar to those in North American and European counties [3].

Some risk factors for CRC were documented in the revised expert report from the World Cancer Research Fund, including physical activity, alcohol consumption, body and abdominal fatness, and consumption of vegetables and foods containing fiber [4]. A recent meta-analysis confirmed that smoking was significantly associated with CRC incidence and mortality [5]. In epidemiologic studies of the Japanese population, the risk factors of physical activity [6,7], alcohol consumption [8,9], smoking habit [8,9], and body mass index (BMI) [9,10] were consistently identified, whereas consumption of vegetables [11] and foods containing fiber [12] were not. Systematic reviews of large studies in Japan also verified the findings for alcohol consumption [13] and smoking habit [14]. In the Japanese population, however, these risk factors were more prevalent in men than in women, and little evidence of modifying CRC risk by reproductive factors has been found among Japanese women [15,16]. Nevertheless, most of these established risk factors for CRC are modifiable, and their improvement has been incorporated into primary cancer prevention strategies in Japan [17].

Given the high incidence of CRC and its significant cost to society, it is critical to reduce the identified risk factors in order to prevent CRC in a population. An individual's risk probability of developing CRC could be estimated by using information on established factors, which would aid physicians and individuals in improving lifestyle behavior and/or deciding on screening regimens for CRC prevention [17–19]. Moreover, from the public health point of view, risk prediction tools could also be used to effectively disseminate information on cancer prevention.

Several studies estimated the absolute risk probability of developing CRC, although they were based on case–control study [18], expert opinion [20], or specific populations [21,22]. In this paper, we present a CRC risk prediction model in Japanese men, derived and validated by two large cohorts from the Japan Public Health Center-based (JPHC) Prospective Study. We also present a simplified score model that can be easily used to estimate an individual's absolute CRC risk based on lifestyle information.

* Corresponding author. Tel.: +81 3 3542 2511x3378; fax: +81 3 3547 8578.
E-mail address: ssasazuk@ncc.go.jp (S. Sasazuki).

1877-7821/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.canep.2010.04.021

2. Materials and methods

2.1. Study participants

In the JPHC Study, Cohort I, with participants aged 40–59 years, was launched in 1990 and Cohort II, with participants aged 40–69 years, was added in 1993. A total of 48,448 men were initially identified in 11 public health center-based (PHC) areas throughout Japan. The details of the study design and baseline response have been described elsewhere [23,24]. The study was approved by the Institute Review Board of the National Cancer Center, Tokyo, Japan.

The baseline survey for Cohort II had more comprehensive data on physical activity and the food frequency questionnaire (FFQ) (52 food items) than those and the FFQ (44 food items) for Cohort I. In the 5-year follow-up survey, all investigations including the FFQ (138 food items) were the same for both cohorts. Considering the inconsistency of questionnaires and follow-up periods of the two cohorts, in the present study we used the baseline survey of Cohort II men to derive the risk prediction model of CRC and the 5-year follow-up survey of Cohort I men to validate the model.

Participants who reported a history of cancer or cardiovascular disease, were diagnosed with cancers, or were censored before the start of the follow-up survey were excluded, leaving 28,115 eligible subjects for model derivation in Cohort II and 18,256 for model validation in Cohort I.

2.2. Risk factor measurements

Self-administered questionnaires contained items on demographic characteristics, medical history, smoking habit, alcohol consumption, physical activity, occupation, and other factors, as well as diets by validated FFQs [25,26].

BMI was calculated as weight in kilograms divided by the square of height in meters. Physical activity levels, measured by metabolic equivalent (MET) hours per day, were estimated by multiplying the reported time spent at each activity per day by its assigned MET intensity: heavy physical work or strenuous exercise (4.5), walking or standing (2.0), sedentary (1.5), and sleep or others (0.9) [6,27]. Daily physical activity level was the sum of MET-hour scores across all activities.

Smoking habit was grouped into never, former, and current smokers. Alcohol consumption was categorized into four groups (never, occasional, regular <300 g/week, and regular ≥300 g/week), in which regular drinkers were categorized by multiplying the frequency per week by the usual daily amount of alcohol consumed [8].

Daily food intake was calculated by multiplying the frequency by standard portion size and relative size for each food item in the FFQ. Daily intake of nutrients was calculated using the 5th revised edition of the Standard Tables of Food Composition in Japan [28].

2.3. Follow-up and case assessment

Participants were followed until 31 December 2005. Residence status, movement of households, and survival were confirmed annually using the residential registers. Information on the cause of death was obtained by examining the death certificates provided by the Ministry of Health, Labour, and Welfare. The occurrence of cancer was identified by active patient notification through the major local hospitals in the study areas and data linkage with population-based cancer registries. The site and histology of each cancer were coded using the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3), with C18–C20 for CRC, C180–C189 for colon cancer, and C199 and C209 for rectal cancer.

2.4. Statistical analysis

Person-years of follow-up were counted from the date of survey response (1993 for Cohort II and 1995 for Cohort I) until the date of CRC diagnosis, the date of moving out of a study area, the date of death, or the end of 2005, whichever came first. Persons lost to follow-up were censored on the last confirmed date of their presence in the study area. Extreme values of height (<100 or >199 cm), weight (<20 kg), and BMI (<14 or >40 kg/m^2) were removed from this analysis. Nutrient intakes were categorized into tertiles for all study participants, with the lower tertile as the reference.

2.4.1. Prediction model derived by JPHC Cohort II

Cox proportional hazards models were derived after testing for the assumptions underlying its use. Then the model of predictive risk of developing CRC was fitted, in which the average survival rates at follow-up time points were estimated by baseline hazard function with mean values of potential predictors. Hazard ratios (HR) and 95% confidential interval (CI) of each risk factor were also estimated. Based on the previous publications in Japanese populations and age-adjusted univariate analysis performed for available variables in this study (including more than 30 food items and nutrients), the potential predictors were applied for building the full multivariate model, which including age, BMI, daily physical activity, alcohol consumption, smoking habit, family history of CRC, and diabetes diagnosed, and interested interaction terms with biological plausibility between alcohol and smoking, and physical activity and BMI. PHC areas were treated as strata in the analysis; assessment of likely shrinkage (over-fitting) was evaluated for the reduced models by $[LR-(p-q)-q]/[LR-(p-q)]$, where LR denotes the likelihood ratio χ^2, and p and q denote the regression degrees of freedom for the full model and for a reduced model, respectively [29]. Non-linear relationships (transformations) of age, BMI, or daily physical activity were tested by using multiple fractional polynomial method of two degree [30,31], however, none of which had been statistically significant for leaving in the model.

For each risk factor, the regression coefficients of two cohorts were compared by a 2-tailed Z statistics, $Z=(\beta_{[d]}-\beta_{[v]})/SE$, where $\beta_{[d]}$ and $\beta_{[v]}$ are the regression coefficients of Cohort II and Cohort I, respectively, and SE is the standard error of the difference in the coefficients, calculated as $\sqrt{(SE^2_{\beta_{[d]}}+SE^2_{\beta_{[v]}})}$ [32]. The Z statistic was used to test the difference in HR of each risk factor/category between the two cohorts [32]. The individual risk of CRC was estimated based on the baseline hazard function of the Cox regression model derived from Cohort II, which method was same as one developed in Framingham heart study [33], where $P=1-S(t)^{\exp(\beta[x,M])}$ and $\beta(x,M)=\beta1(x1-M1)+\ldots+\beta j(xj-Mj)$. $\beta1,\ldots,\beta j$ are the regression coefficients, $x1,\ldots,xj$ represent an individual's risk factors, $M1,\ldots,Mj$ are the mean values of the risk factors in the cohort (for category variables, $x1,\ldots,xj$ are the dichotomous value of the created dummy variable for each category, entering 1 if the individual's value fits that certain category and 0 otherwise, and $M1,\ldots,Mj$ are the proportion of the certain category of the variable in the cohort), and $S(t)$ is the average survival rate at time t of subjects with the mean values of the risk factors used in the Cox model. This procedure performed a better validity than prepared by Ederer method [34]. The predicted 10-year risk of CRC, therefore, was estimated by the baseline hazard function of Cohort II with mean values of each predictor at the 10-year follow-up time.

2.4.2. Prediction model validated by JPHC Cohort I

Discrimination, the ability of a predictive model to separate those who experience an event from those who do not, was

Table 1
Full and reduced predicative models for estimation of developing colorectal cancer events in Cohort II men, Japan Public Health Center-based Prospective Study, 1993–2005.

Variables retained	Full model			Reduced 1[a]			Reduced 2[b]		
	β	S.E.(β)	*P*-Value	β	S.E.(β)	*P*-Value	β	S.E.(β)	*P*-Value
CRC[c]									
Age, year	0.079	0.006	<0001	0.080	0.006	<0001	0.080	0.006	<0001
BMI, kg/m^2	0.001	0.061	0.98	0.047	0.016	<0.01	0.047	0.016	<0.01
Physical activity, MET-h/d	−0.055	0.049	0.27	−0.019	0.006	<0.01	−0.019	0.006	0.01
Family history of CRC (yes)	−0.085	0.382	0.82	−0.087	0.382	0.82	–	–	–
Diabetes (yes)	0.103	0.160	0.52	0.095	0.160	0.55	–	–	–
Alcohol consumption[d]									
Never	0.052	0.244	0.83	−0.163	0.210	0.44	−0.163	0.210	0.44
Regular (<300 g/w)	0.393	0.230	0.09	0.359	0.192	0.06	0.358	0.192	0.06
Regular (≧300 g/w)	0.584	0.273	0.03	0.657	0.195	0.001	0.659	0.195	0.001
Smoking									
Former	−0.165	0.196	0.40	0.070	0.133	0.60	0.071	0.133	0.59
Current	−0.225	0.330	0.50	0.237	0.119	0.05	0.239	0.119	0.04
Smoking × alcohol	0.078	0.056	0.17	–	–	–	–	–	–
BMI × physical activity	0.002	0.002	0.46	–	–	–	–	–	–
d.f.	12			10			8		
Likelihood ratio x^2	239.8			237.3			241.2		
Shrinkage	–			0.96			0.97		
C-Index	0.703			0.699			0.699		
Colon cancer									
Age, year	0.084	0.008	<0001	0.085	0.008	<0001	0.085	0.008	<0001
BMI, kg/m^2	0.037	0.079	0.64	0.048	0.021	0.02	0.049	0.021	0.02
Physical activity, MET-h/d	−0.028	0.063	0.66	−0.019	0.008	0.02	−0.020	0.008	0.01
Family history of CRC (yes)	0.438	0.384	0.25	0.437	0.384	0.26	–	–	–
Diabetes (yes)	0.330	0.188	0.08	0.323	0.188	0.09	–	–	–
Alcohol consumption[d]									
Never	0.077	0.323	0.81	−0.133	0.276	0.63	−0.140	0.276	0.61
Regular (<300 g/w)	0.493	0.305	0.11	0.431	0.253	0.09	0.419	0.254	0.10
Regular (≧300 g/w)	0.651	0.363	0.07	0.657	0.257	0.01	0.655	0.258	0.01
Smoking									
Former	−0.006	0.258	0.98	0.180	0.173	0.30	0.186	0.173	0.28
Current	−0.012	0.433	0.98	0.341	0.157	0.03	0.347	0.157	0.03
Smoking × alcohol	0.057	0.073	0.44	–	–	–	–	–	–
BMI × physical activity	0.000	0.003	0.90	–	–	–	–	–	–
d.f.	12			10			8		
Likelihood ratio x^2	165.7			165.1			166.0		
Shrinkage	–			0.94			0.95		
C-Index	0.710			0.710			0.708		
Rectal cancer									
Age, year	0.072	0.009	<0001	0.071	0.009	<0001	0.067	0.009	<0001
BMI, kg/m^2	−0.054	0.098	0.58	0.033	0.025	0.19	–	–	–
Physical activity, MET-h/d	−0.097	0.078	0.22	−0.018	0.010	0.07	−0.020	0.008	0.02
Diabetes (yes)	−0.357	0.311	0.25	−0.078	0.240	0.75	–	–	–
Alcohol consumption[d]									
Never	0.027	0.374	0.94	−0.401	0.291	0.17	−0.094	0.361	0.80
Regular (<300 g/w)	0.261	0.349	0.45	0.083	0.259	0.75	0.365	0.335	0.28
Regular (≧300 g/w)	−0.536	0.514	0.30	0.488	0.268	0.07	0.745	0.281	0.01
Smoking									
Former	−0.3%	0.305	0.19	0.088	0.181	0.63	–	–	–
Current	0.504	0.415	0.22	0.088	0.181	0.63	–	–	–
Smoking × alcohol	0.109	0.087	0.21	–	–	–	–	–	–
BMI × physical activity	0.003	0.003	0.31	–	–	–	–	–	–
d.f.	11			9			5		
Likelihood ratio χ^2	82.9			80.0			75.7		
Shrinkage	–			0.89			0.94		
C-Index	0.698			0.678			0.678		

[a] Removed interactions.
[b] Further removed family history and diabetes diagnosed for CRC and colon cancer; diabetes diagnosed, BMI, and smoking habit for rectal cancer.
[c] CRC, colorectal cancer; MET, metabolic equivalent.
[d] Occasional alcohol consumption was as the reference.

assessed using the *C* statistic, the area under the receiver operating characteristic curve [32]. The overall *C* statistics and its 95% CIs were calculated by logistic regressions. Calibration is another measure of performance of a prediction model that tests how closely predicted outcomes agree with actual outcomes [32,35]. The calibration was conducted in Cohort I, using the β coefficients, the mean of each risk factor, and the average survival rate at 10-year from the original Cohort II. Participants in Cohort I were divided into 10 deciles of individual predicted risk, and in each decile the expected events were the sum of individual predicted

Table 2
Characteristics of risk factors, person-years of follow-up, and colorectal cancer events in men, Japan Public Health Center-based Prospective Study, 1993–2005[a].

Risk factor	Cohort II[b]						Cohort I[c]					
	Participants, mean (SD), %	No. of participants	Person-years of follow-up	No. of events			Participants, mean (SD), %	No. of participants	Person-years of follow-up	No. of events		
				CRC	Colon	Rectum				CRC	Colon	Rectum
Age, year	52.9(8.8)	28,115	310,059	543	329	214	54.7 (6.0)	18,256	184,496	389	239	150
BMI, kg/m^2	23.4 (2.9)	28,115	310,059	543	329	214	23.6 (2.8)	18,256	184,496	389	239	150
Physical activity, MET-h/d	28.7(7.3)	27,284	300,982	523	314	209	26.8 (7.0)	17,112	173,159	361	219	142
Alcohol consumption												
Never	23.5	6,355	68,967	96	60	36	23.2	4,192	41,652	83	51	32
Occasional	7.7	2,087	23,652	26	15	11	8.6	1,565	16,013	22	10	12
Regular: <300 g/w	48.1	13,038	143,999	248	155	93	35.4	6,403	65,130	108	64	44
Regular: ≧300 g/w	20.8	5,623	62,184	146	85	61	32.9	5,948	60,187	171	111	60
Smoking status												
Never	23.6	6,579	74,342	111	64	47	36.1	6,483	66,178	110	68	42
Former	23.9	6,657	73,238	142	89	53	16.2	2,901	29,256	78	57	21
Current	52.5	14,601	159,481	284	174	110	47.7	8,555	85,836	195	112	83

[a] CRC, colorectal cancer; MET, metabolic equivalent.
[b] Cohort II (follow-up: 1993–2005) was used to develop the prediction model.
[c] Cohort I (follow-up: 1995–2005) was to evaluate the prediction model's performance.

risk [36]. The Hosmer–Lemeshow χ^2 test was applied to analyze the difference between the observed and estimated risk by groups of deciles [37]. The ratio of observed and expected CRC events (the sum of individual predicted risk probability in a certain risk category) was used to test the model predictive capability for each risk factor in Cohort I. The 95% CIs for O/E ratio was calculated as $(O/E) \times \exp[\pm 1.96\sqrt{(1/O)}]$; the prediction model underestimated the CRC risk if the O/E ratio was >1, while it overestimated the risk if the O/E ratio was <1 [36].

2.4.3. Simple point score model

A simple point score model (risk sheet) for CRC was developed based on the original prediction model, with the transference of continuous variables of age, BMI, and physical activity into category variables [38,39]. The β coefficients were newly fitted by the Cox model with each of category variables. The first step was to round regression coefficients to scores, and in this analysis, we multiplied coefficients by three, and round them [38,40]. Further, the risk score of each participant was assigned by summing the points from each risk factor present. The score sheets provide comparison 10-year absolute risks for persons of the same age from average and low-risk CRC.

All analyses were conducted using SAS version 9.01 (SAS Inc., Cary, NC, USA).

3. Results

As of December 2005, newly diagnosed cases of CRC were 543 in Cohort II and 389 in Cohort I. In total, 310,059 and 184,496 person-years were observed in the average follow-up periods of 11.0 and of 10.1 years in Cohorts II and I, respectively.

Comparisons of model constructions among the full predictive model and the models with reduced variables were shown in Table 1, in which the reduced multivariate model with age, BMI, physical activity, smoking habit and alcohol consumption was the optimal one (the global test for model non-proportionality, $P = 0.984$, 0.597, and 0.093 for CRC, colon, and rectal cancer, respectively). Numbers of participants, person-years of follow-up, and CRC events, as well as the risk factors of CRC are listed in Table 2. The respective β coefficients and HRs for CRC risk factors obtained from Cox regression of Cohorts II and I, with baseline survival rate at 10-years, are shown in Table 3. Risk factors showed similar relationships to CRC, colon, and rectal cancer.

In the discriminatory analysis of Cohort II, the C statistics were 0.70 (95% CI, 0.68–0.72) for CRC, 0.71 (95% CI, 0.68–0.74) for colon cancer, and 0.68 (95% CI, 0.64–0.71) for rectal cancer, showing a good ability to distinguish cases from non-cases. In Cohort I, the C statistics were 0.64 (95% CI, 0.61–0.67) for CRC, 0.66 (95% CI: 0.62–0.70) for colon cancer, and 0.62 (95% CI: 0.57–0.66) for rectal cancer, showing a modest ability to distinguish cases from non-cases.

In the calibration analysis, χ^2 was 14.2 ($P = 0.08$) for CRC, 11.0 ($P = 0.20$) for colon, and 11.2 ($P = 0.19$) for rectum cancer, showing that the actual rates of CRC in Cohort I were similar to the rates predicted by the Cohort II function (Fig. 1). The overall O/E ratios were 1.09 (95% CI, 0.98–1.23) for CRC, 1.19 (95% CI, 1.03–1.37) for colon cancer, and 0.94 (95% CI, 0.78–1.12) for rectal cancer. Agreement between the predicted and the observed number of events was good in most risk factor categories with several exceptions (e.g., underestimation for CRC in the "never" alcohol consumption category and overestimation for rectal cancer in the age group of 45–49) (Table 4).

In addition, when participants who had a history of diabetes (1991 in Cohort II and 1332 in Cohort I) or a family history of CRC in first-degree relatives (475 in Cohort II and 157 in Cohort I) were excluded, the same predictive risk factors were identified, and similar discrimination and calibration values were observed for CRC, colon, and rectal cancer, respectively, in Cohort I (data not shown).

The simple point score model (risk sheet) was developed for CRC in Cohort II (Fig. 2), for which the C statistic was 0.69 (95% CI, 0.67–0.71). In Fig. 2, the average and the lowest risk probability by age groups in Cohort II are also shown. Correspondingly, validation was performed in Cohort I for the simple point score model: the C statistic was 0.61 (95% CI, 0.58–0.64) for CRC, with similar O/E ratios and 95% CIs in each category of risk factors (data not shown).

4. Discussion

We developed a CRC risk prediction model with established risk factors of age, BMI, alcohol consumption, smoking status, and physical activity level for middle-aged Japanese men. The prediction model was well calibrated in an external cohort. We also presented a simple point score model (risk sheet) for CRC risk estimation.

Cancer is a multifactorial disease involving a variety of factors in the development of clinical manifestations. This recognition has

Table 3
β-Coefficients and hazard ratios with 95% confidence intervals of colorectal cancer risk factors in men, Japan Public Health Center-based Prospective Study, 1993–2005[a].

Risk factor	Cohort II[b,d]						Cohort I[c,d]					
	CRC		Colon		Rectum		CRC		Colon		Rectum	
	β	HR (95% CI)	β	HR (95% CI)	β	HR (95%CI)	β	HR (95% CI)	β	HR (95% CI)	β	HR (95% CI)
Age, year	0.080	1.08 (1.07–1.10)	0.085	1.09 (1.07–1.11)	0.067	1.07 (1.05–1.09)	0.063	1.07 (1.05–1.09)	0.062	1.06 (1.04–1.09)	0.065	1.07 (1.04–1.10)
BMI, kg/m^2	0.047	1.05 (1.02–1.08)	0.049	1.05 (1.01–1.09)	-	-	0.003	1.00 (0.97–1.04)	0.013	1.01 (0.97–1.06)	-	-
Physical activity, MET-h/d	−0.019	0.98 (0.97–0.99)	−0.020	0.98 (0.97–1.00)	−0.020	0.98 (0.97–1.00)	−0.017	0.98 (0.97–1.00)	−0.027	0.97 (0.95–0.99)	−0.006	0.99 (0.97–1.02)
Alcohol consumption												
Never	−0.163	0.85 (0.56–1.28)	−0.140	0.87 (0.51–1.49)	−0.149	0.86 (0.48–1.55)	0.314	1.37 (0.88–2.14)	0.474	1.61 (0.88–2.92)	−0.028	0.97 (0.51–1.87)
Occasional		1.00		1.00		1.00		1.00		1.00		1.00
Regular: <300 g/w	0.358	1.43 (0.98–2.09)	0.419	1.52 (0.93–2.50)	0.309	1.36 (0.80–2.31)	0.072	1.07 (0.69–1.67)	0.182	1.20 (0.67–2.16)	−0.197	0.82 (0.43–1.55)
Regular: ≧300 g/w	0.659	1.93 (1.32–2.83)	0.655	1.93 (1.16–3.19)	0.745	2.11 (1.21–3.65)	0.679	1.97 (1.30–3.00)	0.858	2.36 (1.35–4.14)	0.348	1.42 (0.76–2.63)
Smoking status												
Never		1.00		1.00				1.00		1.00		
Former	0.071	1.07 (0.83–1.39)	0.186	1.21 (0.86–1.69)	-	-	0.438	1.55 (1.15–2.09)	0.605	1.83 (1.27–2.64)	-	-
Current	0.239	1.27 (1.01–1.60)	0.347	1.41 (1.04–1.92)	-	-	0.323	1.38 (1.08–1.77)	0.222	1.25 (0.91–1.72)	-	-
Baseline survival function at 10-year, S(10)	0.9882		0.9928		0.9954		0.9835		0.9890		0.9942	

[a] CRC, colorectal cancer; HR, hazard ratio; CI, confidential interval; MET, metabolic equivalent.
[b] Cohort II (follow-up: 1993–2005) was used to develop the prediction model.
[c] Cohort I (follow-up: 1995–2005) was to evaluate the prediction model's performance.
[d] The HR of each risk factor/category was not significantly different between Cohort II and Cohort I ($P > 0.05$) for the model of CRC, colon, and rectal cancer, respectively.

Fig. 1. The 10-year observed and predicted colorectal cancer events in Cohort I men, Japan Public Health Center-based Prospective Study, 1993–2005.

led the development of risk assessment tools that attempt to synthesize the values of numerous variables into a single statement about the risk of developing a cancer [41]. In this prediction model, age, alcohol consumption, and daily physical activity level were identified as the most important CRC risk factors, consistent with other reports [4,18,20]. Although body weight was also a potential predictor in this analysis, BMI was arbitrarily selected in the model building as a relevant comprehensive risk factor of CRC [10,18,20].

Dietary factors such as consumption of red meat, green vegetables, fibers, dairy, calcium supplement use, or intake of folate were not identified in this population, although they were previously reported as possibly related to CRC risk [4,18,42]. Moreover, no dietary food combinations, including total meat (pork, beef, bacon, ham, and sausage) [42], processed meat (bacon, ham, and sausage) [42,43], total white meat (fish and poultry) [42], ratio of red meat to vegetable, or ratio of red meat to white meat [44] were risk predictors of CRC in this study population. Although in recent years the dietary pattern in the Japanese population has tended toward the western pattern, the traditional dietary habits were substantially maintained, especially in older people [45]. This may account for the lack of foods or dietary nutrients serving as significant factors for predicting CRC in men. Alternatively, it might be possible that data in this study population were insufficient to support a quantitative statement about the exact magnitude of risk from these diets.

A previous CRC risk prediction model was developed by means of larger case–control studies and included CRC screening during the previous 3 years and number of relatives with CRC [18]. In our study, sigmoidoscopy/colonoscopy and fecal occult blood test were not available in the Cohort II questionnaire, although these are known as indicators for the secondary prevention for CRC [46]. The personal history of diabetes was reported as a possible risk factor of CRC [26]. In the present study, however, diabetes showed statistical significance for colon cancer in the univariate analysis but not in the multivariate analysis. In addition, few participants reported a family history of CRC, such that this factor could not be considered for entering into the prediction model. In the analysis for participants without history of diabetes or family history of CRC, a similar predictive ability for CRC was observed. This may indicate that these two factors were not powerful enough for prediction of CRC in this population. Nevertheless, most CRC risk factors included in this prediction model represent lifestyle choices that can be modified with the aim of preventing the disease.

Several validation studies on cancer risk prediction models also showed modest discriminatory accuracy as measured by *C*

Table 4
10-Years of observed and expected colorectal cancer events, ratios and 95% confidential intervals in Cohort I men, Japan Public Health Center-based Prospective Study, 1993–2005[a].

	CRC					Colon					Rectum				
	Observed	Expected	*O/E* ratio	95%	CI	Observed	Expected	*O/E* ratio	95	%CI	Observed	Expected	*O/E* ratio	95%	CI
Overall	322	294	1.09	0.98	1.23	215	181	1.19	1.03	1.37	107	114	0.94	0.78	1.12
Age, years															
45–49	45	39.0	1.15	0.84	1.58	35	22.8	1.53	1.02	2.31	10	16.4	0.61	0.38	0.99
50–54	62	53.2	1.17	0.89	1.53	41	31.8	1.29	0.91	1.82	21	21.4	0.98	0.64	1.50
55–59	95	76.1	1.25	1.00	1.56	55	46.7	1.18	0.88	1.57	40	29.5	1.36	0.95	1.95
60–64	112	119.9	0.93	0.78	1.12	78	75.9	1.03	0.82	1.29	34	44.7	0.76	0.57	1.02
65–69	8	6.2	1.30	0.59	2.86	6	4.0	1.52	0.57	4.07	2	2.3	0.87	0.24	3.14
BMI, kg/m^2															
<25	230	200.9	1.14	1.00	1.31	153	123.6	1.24	1.04	1.48	–	–	–	–	–
≧25	92	93.5	0.98	0.80	1.21	62	57.6	1.08	0.83	1.39	–	–	–	–	–
Physical activity, MET-h/d															
<22.0	118	109.3	1.08	0.89	1.30	92	67.8	1.36	1.07	1.72	33	41.9	0.79	0.58	1.07
22.0-<28.9	95	101.4	0.94	0.77	1.14	70	62.4	1.12	0.87	1.44	34	39.4	0.86	0.63	1.18
≧28.9	83	83.6	0.99	0.80	1.23	57	50.9	1.12	0.85	1.47	33	33.1	1.00	0.71	1.40
Alcohol consumption															
Never	66	42.5	1.55	1.15	2.10	48	26.0	1.84	1.26	2.71	18	16.5	1.09	0.67	1.77
Occasional	19	17.7	1.07	0.67	1.71	9	10.6	0.85	0.47	1.56	10	6.4	1.57	0.72	3.42
Regular: <300 g/w	95	103.0	0.92	0.76	1.12	59	65.5	0.90	0.71	1.15	36	37.9	0.95	0.69	1.31
Regular: ≧300 g/w	137	129.6	1.06	0.89	1.26	96	78.2	1.23	0.98	1.53	41	53.1	0.77	0.59	1.01
Smoking status															
Never	87	91.6	0.95	0.77	1.17	58	52.7	1.10	0.84	1.44	–	–	–	–	–
Former	69	48.9	1.41	1.07	1.87	52	31.5	1.65	1.16	2.34	–	–	–	–	–
Current	160	149.7	1.07	0.91	1.25	103	94.6	1.09	0.89	1.33	–	–	–	–	–

[a] CRC, colorectal cancer; *O/E*, observed/expected; CI, confidential interval; MET, metabolic equivalent.

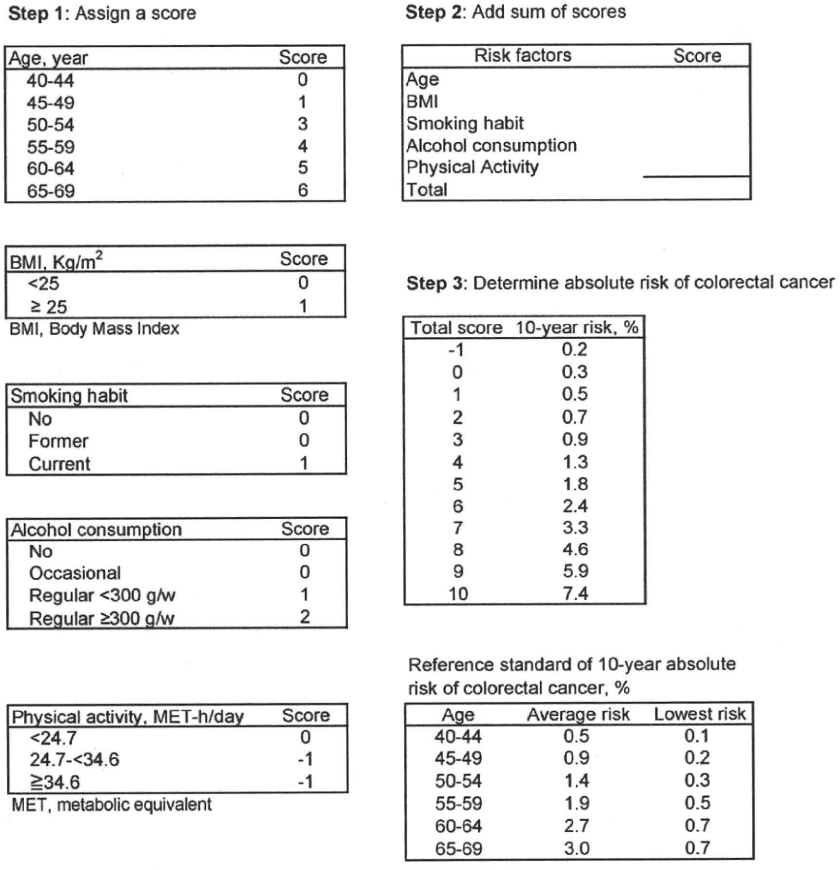


Fig. 2. Simple point score model (risk sheet) for evaluation of 10-year risk of colorectal cancer incidence in men.

statistics, including 0.61 for CRC [36], 0.60–0.63 for breast cancer [47,48], and 0.60–0.69 for lung cancer [49,50]. Similarly, the modest ability to predict CRC in this study suggested that in future studies stronger risk predictors need to be found [18], for instance, dietary nutrient intake or genotypes.

The overall predicted number of CRC events was close to the actual number, with several exceptions in the validation. The differences between the observed and the predicted CRC events in Cohort I may be due to a different distribution of participants with higher risk in the two cohorts. For example, more elderly men and smokers were in Cohort II than in Cohort I, while more heavy alcohol drinkers were in Cohort I than in Cohort II. The discrepancies in the questionnaires used in the two cohorts also may partly account for the difference [36].

The validation in this study was done in an external cohort (Cohort I); however, risk factor profiles and measurement were similar to those of the population for model development (Cohort II). Therefore, the generalizability of the prediction model needs to be tested in other populations to provide more external validations. Another limitation of this study was that the simple point score model (risk sheet) for estimation of CRC risk included not only simple frequency components (age, body weight, and smoking) but also those based on calculation (alcohol consumption by gram per week and physical activity by MET-hour per day). This may make it inconvenient for an individual to use the sheet directly. In addition, because the 5-year follow-up measurement was used as the baseline for Cohort I in this analysis, the smaller relevant population might reduce its validation capability.

In summary, the CRC risk prediction model was developed based on a large cohort study; it showed modest discrimination power and was well calibrated in another large cohort. This model may be used by clinicians, public health professionals, and individuals to estimate the CRC risk for Japanese men, which could play a role in the promotion of CRC prevention strategies. Further validation in other populations, with the addition of more established factors, is necessary.

Conflict of interest statement

None declared.

Acknowledgments

This study was supported by a Grant-in-Aid for Cancer Research (19 shi-2) and for the Third Term Comprehensive 10-year Strategy for Cancer Control (H21-Sanjigan-Ippan-003) from the Ministry of Health, Labour and Welfare of Japan and Grants-in-Aid for Scientific Research for Young Scientists (A) (19689014) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan and Japan Society for the Promotion of Science.

We thank all staff members in each study area for their painstaking efforts to conduct the baseline survey and follow-up. Members of the JPHC Study Group (principal investigator: S. Tsugane) include: S. Tsugane, M. Inoue, T. Sobue, and T. Hanaoka, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo; J. Ogata, S. Baba, T. Mannami, A. Okayama, and Y. Kokubo, National Cardiovascular Center, Suita; K. Miyakawa, F. Saito, A. Koizumi, Y. Sano, I. Hashimoto, T. Ikuta, and Y. Tanaba, Iwate Prefectural Ninohe Public Health Center, Ninohe; Y. Miyajima, N. Suzuki, S. Nagasawa, Y. Furusugi, and N. Nagai, Akita Prefectural Yokote Public Health Center, Yokote; H. Sanada, Y. Hatayama, F. Kobayashi, H. Uchino, Y. Shirai, T. Kondo, R. Sasaki, Y. Watanabe, Y. Miyagawa, Y. Kobayashi, and M. Machida, Nagano Prefectural Saku Public Health Center, Saku; Y. Kishimoto, E. Takara, T. Fukuyama, M. Kinjo, M. Irei, and H. Sakiyama, Okinawa Prefectural Chubu Public Health Center, Okinawa; K. Imoto, H. Yazawa, T. Seo, A. Seiko, F. Ito, F. Shoji, and R. Saito, Katsushika Public Health Center, Tokyo; A. Murata, K. Minato, K. Motegi, and T. Fujieda, Ibaraki Prefectural Mito Public Health Center, Mito; T. Abe, M. Katagiri, M. Suzuki, and K. Matsui, Niigata Prefectural Kashiwazaki and Nagaoka Public Health Center, Kashiwazaki and Nagaoka; M. Doi, A. Terao, Y. Ishikawa, and T. Tagami, Kochi Prefectural Chuo-higashi Public Health Center, Tosayamada; H. Doi, M. Urata, N. Okamoto, F. Ide, and H. Sueta, Nagasaki Prefectural Kamigoto Public Health Center, Arikawa; H. Sakiyama, N. Onga, H. Takaesu, and M. Uehara, Okinawa Prefectural Miyako Public Health Center, Hirara; F. Horii, I. Asano, H. Yamaguchi, K. Aoki, S. Maruyama, M. Ichii, and M. Takano, Osaka Prefectural Suita Public Health Center, Suita; S. Matsushima and S. Natsukawa, Saku General Hospital, Usuda; M. Akabane, Tokyo University of Agriculture, Tokyo; M. Konishi, K. Okada, and I. Saito, Ehime University, Toon; H. Iso, Osaka University, Suita; Y. Honda, K. Yamagishi, S. Sakurai, and N. Tsuchiya, Tsukuba University, Tsukuba; H. Sugimura, Hamamatsu University, Hamamatsu; Y. Tsubono, Tohoku University, Sendai; M. Kabuto, National Institute for Environmental Studies, Tsukuba; S. Tominaga, Aichi Cancer Center Research Institute, Nagoya; M. Iida, W. Ajiki, and A. Ioka, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka; S. Sato, Osaka Medical Center for Health Science and Promotion, Osaka; N. Yasuda, Kochi University, Nankoku; K. Nakamura, Niigata University, Niigata; S. Kono, Kyushu University, Fukuoka; K. Suzuki, Research Institute for Brain and Blood Vessels Akita, Akita; Y. Takashima and M. Yoshida, Kyorin University, Mitaka; E. Maruyama, Kobe University, Kobe; M. Yamaguchi, Y. Matsumura, S. Sasaki, and S. Watanabe, National Institute of Health and Nutrition, Tokyo; T. Kadowaki, Tokyo University, Tokyo; M. Noda and T. Mizoue, International Medical Center of Japan, Tokyo; Y. Kawaguchi, Tokyo Medical and Dental University, Tokyo; H. Shimizu, Sakihae Institute, Gifu.

References

[1] Matsuda T, Marugame T, Kamo K, Katanoda K, Ajiki W, Sobue T. Cancer incidence and incidence rates in Japan in 2002: based on data from 11 population-based cancer registries. Jpn J Clin Oncol 2008;38:641–8.
[2] The Editorial Board of the Cancer Statistics in Japan, ed. Cancer statistics in Japan 2007. Tokyo: Foundation for Promotion of Cancer Research (FPCR), 2007
[3] Shibuya K, Mathers CD, Boschi-Pinto C, Lopez AD, Murray CJ. Global and regional estimates of cancer mortality and incidence by site. II. Results for the global burden of disease 2000. BMC Cancer 2002;2:37.
[4] Wiseman M. The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Proc Nutr Soc 2008;67:253–6.
[5] Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P. Smoking and colorectal cancer: a meta-analysis. JAMA 2008;300:2765–78.
[6] Lee KJ, Inoue M, Otani T, Iwasaki M, Sasazuki S, Tsugane S. Physical activity and risk of colorectal cancer in Japanese men and women: the Japan Public Health Center-based prospective study. Cancer Causes Contr 2007;18:199–209.
[7] Isomura K, Kono S, Moore MA, Toyomura K, Nagano J, Mizoue T, et al. Physical activity and colorectal cancer: the Fukuoka colorectal cancer study. Cancer Sci 2006;97:1099–104.
[8] Otani T, Iwasaki M, Yamamoto S, Sobue T, Hanaoka T, Inoue M, et al. Alcohol consumption, smoking, and subsequent risk of colorectal cancer in middle-aged and elderly Japanese men and women: Japan Public Health Center-based prospective study. Cancer Epidemiol Biomarkers Prev 2003;12:1492–500.
[9] Shimizu N, Nagata C, Shimizu H, Kametani M, Takeyama N, Ohnuma T, et al. Height, weight, and alcohol consumption in relation to the risk of colorectal cancer in Japan: a prospective study. Br J Cancer 2003;88:1038–43.
[10] Otani T, Iwasaki M, Inoue M. Body mass index, body height, and subsequent risk of colorectal cancer in middle-aged and elderly Japanese men and women: Japan public health center-based prospective study. Cancer Causes Contr 2005;16:839–50.
[11] Tsubono Y, Otani T, Kobayashi M, Yamamoto S, Sobue T, Tsugane S. No association between fruit or vegetable consumption and the risk of colorectal cancer in Japan. Br J Cancer 2005;92:1782–4.
[12] Otani T, Iwasaki M, Ishihara J, Sasazuki S, Inoue M, Tsugane S. Dietary fiber intake and subsequent risk of colorectal cancer: the Japan Public Health Center-based prospective study. Int J Cancer 2006;119:1475–80.
[13] Mizoue T, Inoue M, Wakai K, Nagata C, Shimazu T, Tsuji I, et al. Alcohol drinking and colorectal cancer in Japanese: a pooled analysis of results from five cohort studies. Am J Epidemiol 2008;167:1397–406.

[14] Mizoue T, Inoue M, Tanaka K, Tsuji I, Wakai K, Nagata C, et al. Tobacco smoking and colorectal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. Jpn J Clin Oncol 2006;36:25–39.
[15] Akhter M, Inoue M, Kurahashi N, Iwasaki M, Sasazuki S, Tsugane S. Reproductive factors, exogenous female hormone use and colorectal cancer risk: the Japan Public Health Center-based Prospective Study. Eur J Cancer Prev 2008;17:515–24.
[16] Tamakoshi K, Wakai K, Kojima M, Watanabe Y, Hayakawa N, Toyoshima H, et al. A prospective study of reproductive and menstrual factors and colon cancer risk in Japanese women: findings from the JACC study. Cancer Sci 2004;95:602–7.
[17] Tsugane S. What we know about associations between diet and cancer. JMAJ 2008;51:7.
[18] Freedman AN, Slattery ML, Ballard-Barbash R, Willis G, Cann BJ, Pee D, et al. Colorectal cancer risk prediction tool for white men and women without known susceptibility. J Clin Oncol 2008.
[19] Parkin DM, Olsen AH, Sasieni P. The potential for prevention of colorectal cancer in the UK. Eur J Cancer Prev 2009;18:179–90.
[20] Colditz GA, Atwood KA, Emmons K, Monson RR, Willett WC, Trichopoulos D, et al. Harvard report on cancer prevention volume 4: Harvard cancer risk index. Risk Index Working Group, Harvard Center for Cancer Prevention. Cancer Causes Contr 2000;11:477–88.
[21] Selvachandran SN, Hodder RJ, Ballal MS, Jones P, Cade D. Prediction of colorectal cancer by a patient consultation questionnaire and scoring system: a prospective study. Lancet 2002;360:278–83.
[22] Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Using risk for advanced proximal colonic neoplasia to tailor endoscopic screening for colorectal cancer. Ann Intern Med 2003;139:959–65.
[23] Tsugane S, Sobue T. Baseline survey of JPHC study—design and participation rate. Japan public health center-based prospective study on cancer and cardiovascular diseases. J Epidemiol 2001;11:S24–9.
[24] Iwasaki M, Otani T, Yamamoto S, Inoue M, Hanaoka T, Sobue T, et al. Background characteristics of basic health examination participants: the JPHC study baseline survey. J Epidemiol 2003;13:216–25.
[25] Sasaki S, Kobayashi M, Ishihara J, Tsugane S. Self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC study: questionnaire structure, computation algorithms, and area-based mean intake. J Epidemiol/Jpn Epidemiol Assoc 2003;13:S13–22.
[26] Inoue M, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. Arch Intern Med 2006;166:1871–7.
[27] Inoue M, Iso H, Yamamoto S, Kurahashi N, Iwasaki M, Sasazuki S, et al. Daily total physical activity level and premature death in men and women: results from a large-scale population-based cohort study in Japan (JPHC study). Ann Epidemiol 2008;18:522–30.
[28] Technology. CfSa, Ministry of Education C., Sports, Science and Technology the Government of Japan, ed. Standard tables of food composition in Japan, the fifth revised and enlarged edition. Tokyo: Printing Bureau, Ministry of Finance, 2005.
[29] Harrell Jr FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361–87.
[30] Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. Int J Epidemiol 1999;28:964–74.
[31] Sauerbrei W, Meier-Hirmer C, Benner A, Royston P. Multivariable regression model building by using fractional polynomials: description of SAS, STATA and R programs. Comput Stat Data Anal 2006;50:3464–85.
[32] Liu J, Hong Y, D'Agostino Sr RB, Wu Z, Wang W, Sun J, et al. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. JAMA 2004;291:2591–9.
[33] D'Agostino Sr RB, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 2001;286:180–7.
[34] Therneau TM, Grambsch GP. Expected survival. Modeling survival data: extending the Cox model. Springer; 2004. p. 280.
[35] D'Agostino RB, Nam BH. Evaluation of the performance of survival analysis models: discrimination and calibration measures. In: Balakrishnan NRC, ed. Handbook of statistics, vol. 23. London, England: Elsevier, 2004.
[36] Park Y, Freedman AN, Gail MH, Pee D, Hollenbeck A, Schatzkin A, et al. Validation of a colorectal cancer risk prediction model among white patients age 50 years and older. J Clin Oncol 2009;27:694–8.
[37] Lemeshow S, Hosmer Jr DW. A review of goodness of fit statistics for use in the development of logistic regression models. Am J Epidemiol 1982;115:92–106.
[38] Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837–47.
[39] Wu Y, Liu X, Li X, Li Y, Zhao L, Chen Z, et al. Estimation of 10-year risk of fatal and nonfatal ischemic cardiovascular diseases in Chinese adults. Circulation 2006;114:2217–25.
[40] Steyerberg EW. Clinical prediction models: a practical approach to development, validation, and updating. Springer; 2009.
[41] Kannel WB, McGee DL. Composite scoring—methods and predictive validity: insights from the Framingham Study. Health Serv Res 1987;22:499–535.
[42] Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC. Intake of fat, meat, and fiber in relation to risk of colon cancer in men. Cancer Res 1994;54:2390–7.
[43] Cross AJ, Leitzmann MF, Gail MH, Hollenbeck AR, Schatzkin A, Sinha R. A prospective study of red and processed meat intake in relation to cancer risk. PLoS Med 2007;4:e325.
[44] McCullough ML, Feskanich D, Stampfer MJ, Giovannucci EL, Rimm EB, Hu FB, et al. Diet quality and major chronic disease risk in men and women: moving toward improved dietary guidance. Am J Clin Nutr 2002;76:1261–71.
[45] Kim MK, Sasaki S, Sasazuki S, Tsugane S. Prospective study of three major dietary patterns and risk of gastric cancer in Japan. Int J Cancer 2004;110:435–42.
[46] Lee KJ, Inoue M, Otani T, Iwasaki M, Sasazuki S, Tsugane S. Colorectal cancer screening using fecal occult blood test and subsequent risk of colorectal cancer: a prospective cohort study in Japan. Cancer Detect Prev 2007;31:3–11.
[47] Chen J, Pee D, Ayyagari R, Graubard B, Schairer C, Byrne C, et al. Projecting absolute invasive breast cancer risk in white women with a model that includes mammographic density. J Natl Cancer Inst 2006;98:1215–26.
[48] Barlow WE, White E, Ballard-Barbash R, Vacek PM, Titus-Ernstoff L, Carney PA, et al. Prospective breast cancer risk prediction model for women undergoing screening mammography. J Natl Cancer Inst 2006;98:1204–14.
[49] Rosner BA, Colditz GA, Webb PM, Hankinson SE. Mathematical models of ovarian cancer incidence. Epidemiology 2005;16:508–15.
[50] Cronin KA, Gail MH, Zou Z, Bach PB, Virtamo J, Albanes D. Validation of a model of lung cancer risk prediction among smokers. J Natl Cancer Inst 2006;98:637–40.

Cancer Research

Interaction between Adiponectin and Leptin Influences the Risk of Colorectal Adenoma

Taiki Yamaji, Motoki Iwasaki, Shizuka Sasazuki, and Shoichiro Tsugane

Abstract

Obesity has been associated with an increased risk of colorectal neoplasia, but the mechanisms of this potential association have not been elucidated. We hypothesized that the adipokines adiponectin, leptin, and tumor necrosis factor-α (TNF-α) may mediate an association between obesity and colorectal cancer. We measured plasma concentrations of total and high-molecular-weight (HMW) adiponectin, leptin, and TNF-α in healthy volunteer examinees who underwent total colonoscopy between February 2004 and February 2005, and conducted a case-control study consisting of 778 cases and 735 controls. An inverse association of total and HMW adiponectin was observed with colorectal adenoma (P trend < 0.001 and 0.03, respectively). Further, total adiponectin interacted with leptin, but not TNF-α, in relation to colorectal adenoma (P interaction = 0.007). An inverse association of total adiponectin with colorectal adenoma was apparent in the highest two tertiles of leptin, particularly the middle (P trend < 0.001), whereas a positive association of leptin was obvious in the lowest tertile of total adiponectin (P trend = 0.01) after adjusting for potential confounders and body mass index, which is a major determinant of insulin resistance. Adiponectin may exert an anticarcinogenic effect on the large intestine by interfering with leptin, whereas leptin could conversely exert a carcinogenic effect under conditions of a lower abundance of adiponectin. Our findings provide the first epidemiologic evidence for interactive effects of adiponectin and leptin in the early stage of colorectal tumorigenesis, distinct from their involvement in insulin resistance. *Cancer Res; 70(13); 5430–7. ©2010 AACR.*

Introduction

Overweight and obesity have been consistently associated with an increase in the risk of colorectal cancer and adenoma, a well-established precursor lesion of colorectal cancer (1). However, the mechanisms of this potential association between adiposity and colorectal neoplasia have not been fully elucidated. Adipose tissue, long considered an inert energy storage depot, is now recognized as an active endocrine organ, and in fact releases a wide variety of biologically functional molecules, collectively referred to as adipokines (2). Importantly, accumulating evidence suggests that several adipokines, namely adiponectin, leptin, and tumor necrosis factor-α (TNF-α), have the potential to mediate the association between adiposity and colorectal neoplasia (1). These adipokines are in fact all related to insulin resistance (2), which has been suggested to be an early and fundamental disorder in the path to several obesity-related malignancies, including colorectal cancer (3).

Adiponectin, an insulin-sensitizing hormone, is secreted exclusively by adipocytes, and circulates in plasma in three forms of oligomeric complex: a simple complex of a trimer, a low-molecular-weight complex of two trimers, and a high-molecular-weight (HMW) complex of up to six trimers (3). Although HMW adiponectin is now considered the active form of the hormone, different forms have shown distinct biological effects through differential activation of downstream signaling cascades (3). Besides its well-known effect on insulin resistance, adiponectin seems to directly modulate several intracellular signaling pathways involved in colorectal carcinogenesis (4, 5), probably through the two isoforms of its receptors, adiponectin receptor 1 and 2, which are expressed in normal colon epithelium and colon cancer tissue (6, 7). Further, recent basic research has found that adiponectin inhibits leptin- and TNF-α–induced signaling cascades, both of which lead to cell proliferation and survival (8–11). However, few epidemiologic studies have examined the association of circulating levels of adiponectin with colorectal adenoma (12) and cancer (13–15), and no epidemiologic study has evaluated the interaction of adiponectin with leptin and TNF-α in relation to the risk of colorectal neoplasia.

Here, we measured plasma concentrations of total and HMW adiponectin, leptin, and TNF-α among middle-aged and elderly Japanese men and women, and investigated not only the association of circulating levels of these adipokines with colorectal adenoma but also the interaction of total and

Authors' Affiliation: Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan

Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

Corresponding Author: Taiki Yamaji, Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Phone: 81-3-3542-2511; Fax: 81-3-3547-8578; E-mail: tyamaji@ncc.go.jp.

doi: 10.1158/0008-5472.CAN-10-0178

HMW adiponectin with leptin and TNF-α in relation to the risk of colorectal adenoma.

Materials and Methods

Study population

The Research Center for Cancer Prevention and Screening was established in 2004 as a branch of the National Cancer Center of Japan with the goal of developing preventive methods for various types of cancers. Among its efforts, the Research Center conducted the Colorectal Adenoma Study in Tokyo (16, 17), a case-control study specifically designed to investigate environmental and genetic factors related to the early stage of colorectal carcinogenesis among healthy volunteer examinees of a colorectal cancer screening. All examinees gave written informed consent to allow their data and materials collected through the screening to be used for medical research. The study protocol was approved by the institutional review board of the National Cancer Center.

Eligible subjects were defined in advance as men ages 50 to 79 years and women ages 40 to 79 years who underwent total colonoscopy from the anus to the cecum and who were without a history of colorectal adenoma, any malignant neoplasia, ulcerative colitis, Crohn's disease, familial adenomatous polyposis, carcinoid tumor, or colectomy. Of a consecutive series of 3,212 examinees undergoing magnifying colonoscopy with indigo carmine dye spraying between February 2004 and February 2005, 2,234 met these conditions. Based on the pit pattern of colorectal lesions, namely the characteristics of mucosal crypts, 526 men and 256 women were determined to have at least one adenoma and were thus included as adenoma cases. Pit-pattern classification based on magnifying chromo-endoscopy has been detailed elsewhere (18). Of the remaining 1,452 examinees, we identified 482 men and 721 women as potential controls who were also free from other benign lesions (e.g., hyperplastic polyps, inflammatory polyps, and diverticula). For efficiency, 256 of the potential female controls were frequency-matched to the female cases in five age categories (40–49, 50–54, 55–59, 60–64, and ≥65 years of age) and two screening periods (first and second halves). Because there were fewer potential male controls than male cases, all potential male controls were included in the study. Finally, the study enrolled 782 cases and 738 controls. Cases with adenomas of ≥5 mm in diameter were referred to clinical hospitals for definitive diagnosis and treatment.

Blood collection and laboratory procedures

Examinees were scheduled for blood collection before any cancer screening procedures on the first day of screening. Fasting venous blood was drawn into a vacutainer tube with EDTA. Almost three-quarters of examinees had fasted since the day before the screening day. The blood sample was centrifuged to obtain blood plasma and buffy coat, and these specimens were preserved at −80°C until analysis.

Plasma concentrations of total and HMW adiponectin were measured at Mitsubishi Chemical Medience, Tokyo, Japan, and those of leptin and TNF-α at GeneticLab, Hokkaido, Japan. All laboratory personnel were blinded with respect to case and control status. Plasma concentrations of total and HMW adiponectin were simultaneously analyzed using a Human Adiponectin ELISA Kit for Total and Multimers (Sekisui Medical) by the enzyme-linked immunosorbent assay method. Minimum detection level was 0.39 μg/mL for both total and HMW adiponectin. The kit manufacturer has reported that intra-assay coefficients of variation for total and HMW adiponectin are 5.4% and 5.0%, respectively. Plasma concentrations of leptin and TNF-α were simultaneously assayed using a Human Serum Adipokine (Panel B) LINCO*plex* Kit (Millipore) based on the xMAP Technology (Luminex). Minimum detection levels of leptin and TNF-α were 85.4 and 0.14 pg/mL, respectively. According to the manufacturer, the intra-assay coefficients of variation were reported to be 1.4% to 7.9%.

Self-administered questionnaire and anthropometric measurements

Before cancer screening, all examinees were encouraged to complete a self-administered questionnaire concerning lifestyle and socioeconomic characteristics as well as personal and family medical history. Details of the questionnaire have been described elsewhere (16, 17). In brief, the questionnaire inquired about smoking habits by first determining smoking status (current, past, and never) and then expressing lifetime exposure to cigarette smoking among ever smokers (i.e., past and current smokers) by pack-years, with 1 pack-year defined as the smoking of 20 cigarettes every day for 1 year. The questionnaire also inquired about drinking habits by first determining drinking status (current, past, and never) and then calculating the amount of alcohol consumed per week among current drinkers on the basis of the frequency of alcohol drinking and the number of standard units consumed per occasion for five different alcoholic beverages (sake, *shochu/awamori*, beer, whisky, and wine).

At the beginning of cancer screening, body weight and height were measured by medical personnel, and body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared.

Statistical analysis

An unconditional logistic regression model was used to estimate odds ratios (OR) and their 95% confidence intervals (95% CI) of colorectal adenoma according to sex-specific tertiles of total and HMW adiponectin, leptin, and TNF-α, with the lowest tertile for each adipokine used as the reference. Statistical adjustment was made in three models. Model 1 controlled for matching variables (i.e., age categories and screening periods) and the duration of fasting (from the day before the screening day, from the day of screening), whereas model 2 additionally adjusted for the following covariates: cigarette smoking (never, ≤20, 21–40, and >40 pack-years), alcohol drinking (never, past, <150, 150–299, ≥300 g/wk), family history of colorectal cancer (yes or no), and nonsteroidal anti-inflammatory drug use (yes or no). These covariates were suggested to be potential confounders in previous reports from the Colorectal Adenoma Study in Tokyo (16, 17). Model 3 further adjusted model 2 for BMI (<21.0, 21.0–22.9, 23.0–24.9, and ≥25.0 kg/m^2). Spearman's

Table 1. Selected characteristics of cases and controls by sex

Characteristic	Men			Women		
	Cases (n = 523)	Controls (n = 480)	P difference*	Cases (n = 255)	Controls (n = 255)	P difference*
Categorical variables, n (%)						
≥65 y of age	172 (33)	123 (26)	0.04	61 (24)	61 (24)	0.99
>40 pack-years	136 (26)	68 (14)	<0.001	6 (2)	2 (1)	0.03
≥300 g of alcohol/wk	153 (29)	98 (20)	0.004	6 (2)	8 (3)	0.14
Family history of CRC	72 (14)	65 (14)	0.91	55 (22)	26 (10)	<0.001
NSAID use	21 (4)	40 (8)	0.004	12 (5)	15 (6)	0.55
Overweight and obesity	188 (36)	124 (26)	0.002	46 (18)	37 (15)	0.31
Continuous variables, median (IQR)						
Total adiponectin (μg/mL)	3.98 (3.08–5.21)	4.37 (3.13–5.95)	0.002	6.81 (4.93–8.65)	7.36 (5.07–9.22)	0.21
HMW adiponectin (μg/mL)	1.20 (0.71–1.95)	1.33 (0.77–2.29)	0.02	2.78 (1.76–4.08)	3.01 (1.78–4.26)	0.28
Leptin (pg/mL)	3,333 (1,747–5,357)	2,671 (1,417–4,670)	<0.001	6,237 (3,789–10,739)	5,667 (3,138–9,260)	0.13
TNF-α (pg/mL)	2.70 (2.29–3.20)	2.67 (2.24–3.13)	0.42	2.45 (2.06–2.89)	2.50 (2.08–2.93)	0.42

Abbreviations: CRC, colorectal cancer; NSAID, nonsteroidal anti-inflammatory drug; IQR, interquartile range.
*Based on the χ^2 test for percentage difference and the Wilcoxon rank-sum test for median difference.

correlation coefficients of BMI with total and HMW adiponectin, leptin, and TNF-α were −0.24, −0.23, 0.59, and 0.06, respectively, for male controls, and −0.21, −0.22, 0.64, and 0.18, respectively, for female controls. Linear trends in the ORs of colorectal adenoma were also assessed by assigning ordinal values to tertiles of respective adipokines. Finally, we combined men and women according to sex-specific tertiles of total and HMW adiponectin, leptin, and TNF-α, and examined whether the association between these adipokines and colorectal adenoma was modified by sex. Interaction terms were created between indicator variables representing categories of each adipokine and of sex, and their significance was statistically evaluated based on the likelihood ratio test with two degrees of freedom.

We then examined whether adiponectin interacted with leptin or TNF-α to modify its association with colorectal adenoma. We obtained ORs and 95% CIs of colorectal adenoma for nine combinations of tertiles of adiponectin and of leptin/TNF-α, with reference to the combination of the lowest tertile of adiponectin and the highest tertile of leptin/TNF-α. Finally, we statistically evaluated these interactions based on the likelihood ratio test with four degrees of freedom. Interaction terms were created between indicator variables representing tertiles of adiponectin and of leptin/TNF-α.

Of 1,520 study subjects, 7 had missing information, namely 3 with regard to cigarette smoking and 4 for BMI. These were then excluded, and the current analysis was conducted in 1,003 men (523 cases, 480 controls) and 510 women (255 cases, 255 controls). Of these, 121 and 57 had plasma concentrations of HMW adiponectin and leptin below the minimum detection levels, respectively, and were assigned the putative values of 0.30 μg/mL and 50.0 pg/mL, respectively. Two-sided P values <0.05 were regarded as statistically significant. All statistical analyses were carried out using Statistical Analysis System (SAS), version 9.1 (SAS Institute).

Results

Selected characteristics of cases and controls by sex

Table 1 summarizes selected characteristics of cases and controls by sex. Male cases were more likely to be old and overweight, and tended to consume more cigarettes and alcohol, whereas male controls tended to use more nonsteroidal anti-inflammatory drugs. Female controls were more likely to be never smokers and tended to have less family history of colorectal cancer than female cases. Table 1 also shows plasma concentrations of total and HMW adiponectin, leptin, and TNF-α among cases and controls by sex. Male cases had lower plasma concentrations of total and HMW adiponectin and higher plasma concentrations of leptin than male controls. Of note, we observed substantial sex difference in plasma concentrations of total and HMW adiponectin and leptin. Correlations between total and HMW adiponectin, leptin, and TNF-α are presented in Supplementary Table S1. Total and HMW adiponectin were weakly inversely correlated with leptin, whereas leptin was weakly positively correlated with TNF-α.

Association of total and HMW adiponectin with colorectal adenoma

Table 2 shows the ORs of colorectal adenoma according to sex-specific tertiles of total and HMW adiponectin. In men, we observed a statistically significant trend of decreasing

adjusted ORs for colorectal adenoma across tertiles of total adiponectin (P trend = 0.002), and a marginally significant trend for HMW adiponectin (P trend = 0.08). A significantly reduced OR was also seen among men in the highest tertile of total adiponectin. Adjusted ORs of colorectal adenoma for the highest compared with the lowest tertile were 0.60 (95% CI, 0.44–0.83) and 0.75 (95% CI, 0.54–1.03) for total and HMW adiponectin, respectively. On further adjustment for BMI, the inverse association between total adiponectin and colorectal adenoma was still evident (P trend = 0.01). In women, neither total nor HMW adiponectin was measurably associated with colorectal adenoma, although adjusted ORs of colorectal adenoma for the highest tertile were below unity for both forms of adiponectin. When men and women were combined according to sex-specific tertiles, a significant trend of decreasing adjusted ORs across tertiles was observed for both total and HMW adiponectin (P trend < 0.001 and 0.03, respectively). Although additional adjustment for BMI attenuated the inverse association between both forms of adiponectin and colorectal adenoma, a significant trend across tertiles remained for total adiponectin (P trend = 0.01). The inverse association of total adiponectin remained significant after further adjustment for indicators of energy balance (i.e., total energy intake, physical activity, and height), dietary factors (i.e., intakes of meat; fruits and vegetables; dairy products; folate; vitamins B_2, B_6, and B_{12}; vitamin D; calcium; and total isoflavones), and metabolic factors (i.e., serum concentrations of triglycerides, total cholesterol, and glucose; P trend = 0.02; data not shown). When total and HMW adiponectin levels were treated as a continuous variable in model 2, adjusted ORs of colorectal adenoma for a 1 μg/mL increase were 0.95 (95% CI, 0.92–0.99) and 0.94 (95% CI, 0.88–1.01) for total and HMW adiponectin, respectively (data not shown). In this analysis of HMW adiponectin, 121 subjects

Table 2. Association of total and HMW adiponectin with colorectal adenoma

Measurement	Tertile			P trend*
	Lowest	Middle	Highest	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	
Total adiponectin				
Men, range (μg/mL)	–3.64	3.65–5.26	5.27–	
Model 1†	1.00 (reference)	0.79 (0.59–1.07)	0.55 (0.40–0.76)	<0.001
Model 2‡	1.00 (reference)	0.83 (0.61–1.13)	0.60 (0.44–0.83)	0.002
Model 3§	1.00 (reference)	0.85 (0.62–1.15)	0.66 (0.47–0.92)	0.01
Women, range (μg/mL)	–5.76	5.77–8.49	8.50–	
Model 1†	1.00 (reference)	1.01 (0.66–1.53)	0.69 (0.44–1.08)	0.11
Model 2‡	1.00 (reference)	1.05 (0.68–1.61)	0.80 (0.50–1.27)	0.36
Model 3§	1.00 (reference)	1.07 (0.69–1.65)	0.88 (0.54–1.41)	0.61
Men and women combined				0.68‖
Model 1† ¶	1.00 (reference)	0.86 (0.67–1.09)	0.60 (0.46–0.77)	<0.001
Model 2‡ ¶	1.00 (reference)	0.87 (0.68–1.11)	0.64 (0.49–0.83)	<0.001
Model 3§ ¶	1.00 (reference)	0.89 (0.69–1.14)	0.70 (0.53–0.91)	0.01
HMW adiponectin				
Men, range (μg/mL)	–0.88	0.89–1.91	1.92–	
Model 1†	1.00 (reference)	1.04 (0.77–1.41)	0.71 (0.52–0.98)	0.04
Model 2‡	1.00 (reference)	1.05 (0.78–1.43)	0.75 (0.54–1.03)	0.08
Model 3§	1.00 (reference)	1.08 (0.79–1.47)	0.82 (0.59–1.15)	0.28
Women, range (μg/mL)	–2.19	2.20–3.90	3.91–	
Model 1†	1.00 (reference)	1.13 (0.74–1.71)	0.75 (0.48–1.18)	0.22
Model 2‡	1.00 (reference)	1.17 (0.76–1.80)	0.85 (0.54–1.36)	0.52
Model 3§	1.00 (reference)	1.20 (0.78–1.87)	0.94 (0.58–1.53)	0.85
Men and women combined				0.93‖
Model 1† ¶	1.00 (reference)	1.07 (0.84–1.36)	0.73 (0.56–0.94)	0.01
Model 2‡ ¶	1.00 (reference)	1.07 (0.83–1.36)	0.75 (0.58–0.97)	0.03
Model 3§ ¶	1.00 (reference)	1.10 (0.85–1.40)	0.83 (0.63–1.08)	0.19

*Statistical tests for trend (two-sided) were assessed by assigning ordinal values to tertiles of each measurement.
†Adjusted for age, screening period, and duration of fasting.
‡Model 1 + cigarette smoking, alcohol drinking, family history of colorectal cancer, and nonsteroidal anti-inflammatory drug use.
§Model 2 + BMI.
‖Values are P interaction instead of P trend.
¶Further adjusted for sex.

below the minimum detection levels were excluded. Despite the sex differences in plasma concentrations of adiponectin, a significant effect modification by sex was not seen for either total or HMW adiponectin (P interaction = 0.68 and 0.93, respectively).

Association of leptin and TNF-α with colorectal adenoma

We also investigated the association of leptin and TNF-α with colorectal adenoma (Table 3). When men and women were combined according to sex-specific tertiles of leptin, a significant trend of increasing adjusted ORs across tertiles was observed (P trend < 0.001) with a significantly elevated OR for the highest tertile (OR, 1.57; 95% CI, 1.21–2.02). On additional adjustment for BMI, the positive association between leptin and colorectal adenoma was considerably attenuated (P trend = 0.10). In contrast, no material association was seen between TNF-α and colorectal adenoma. When leptin and TNF-α levels were treated as a continuous variable in model 2, adjusted ORs of colorectal adenoma for a 1 ng/mL increase in leptin and a 1 pg/mL increase in TNF-α were 1.03 (95% CI, 1.01–1.05) and 0.99 (95% CI, 0.96–1.02), respectively (data not shown). In this analysis of leptin, 57 subjects below the minimum detection levels were excluded. Again, effect modification by sex was not observed for either leptin or TNF-α (P interaction = 0.53 and 0.42, respectively).

Association of total and HMW adiponectin with colorectal adenoma according to tertiles of leptin and TNF-α

We then examined whether adiponectin interacted with leptin or TNF-α to modify its association with colorectal

Table 3. Association of leptin and TNF-α with colorectal adenoma

Measurement	Tertile			*P* trend*
	Lowest	Middle	Highest	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	
Leptin				
Men, range (pg/mL)	–1,756	1,757–3,842	3,843–	
Model 1†	1.00 (reference)	1.29 (0.94–1.78)	1.69 (1.24–2.30)	0.001
Model 2‡	1.00 (reference)	1.30 (0.94–1.80)	1.73 (1.26–2.38)	<0.001
Model 3§	1.00 (reference)	1.18 (0.84–1.67)	1.44 (0.99–2.08)	0.05
Women, range (pg/mL)	–3,856	3,857–7,908	7,909–	
Model 1†	1.00 (reference)	1.31 (0.85–2.03)	1.36 (0.88–2.10)	0.18
Model 2‡	1.00 (reference)	1.23 (0.78–1.93)	1.36 (0.87–2.13)	0.18
Model 3§	1.00 (reference)	1.15 (0.71–1.86)	1.11 (0.65–1.92)	0.70
Men and women combined				0.53‖
Model 1† ¶	1.00 (reference)	1.30 (1.00–1.67)	1.55 (1.21–2.00)	<0.001
Model 2‡ ¶	1.00 (reference)	1.28 (0.99–1.66)	1.57 (1.21–2.02)	<0.001
Model 3§ ¶	1.00 (reference)	1.17 (0.89–1.54)	1.29 (0.95–1.74)	0.10
TNF-α				
Men, range (pg/mL)	–2.38	2.39–2.97	2.98–	
Model 1†	1.00 (reference)	1.19 (0.87–1.62)	1.01 (0.74–1.38)	0.97
Model 2‡	1.00 (reference)	1.24 (0.90–1.69)	0.97 (0.70–1.34)	0.85
Model 3§	1.00 (reference)	1.24 (0.90–1.70)	0.94 (0.68–1.30)	0.70
Women, range (pg/mL)	–2.22	2.23–2.79	2.80–	
Model 1†	1.00 (reference)	0.98 (0.64–1.49)	0.74 (0.47–1.15)	0.18
Model 2‡	1.00 (reference)	0.88 (0.56–1.37)	0.69 (0.43–1.10)	0.11
Model 3§	1.00 (reference)	0.85 (0.54–1.33)	0.65 (0.41–1.05)	0.07
Men and women combined				0.42‖
Model 1† ¶	1.00 (reference)	1.11 (0.87–1.42)	0.91 (0.71–1.18)	0.47
Model 2‡ ¶	1.00 (reference)	1.15 (0.89–1.48)	0.88 (0.68–1.14)	0.34
Model 3§ ¶	1.00 (reference)	1.13 (0.88–1.46)	0.85 (0.65–1.10)	0.21

*Statistical tests for trend (two-sided) were assessed by assigning ordinal values to tertiles of each measurement.
†Adjusted for age, screening period, and duration of fasting.
‡Model 1 + cigarette smoking, alcohol drinking, family history of colorectal cancer, and nonsteroidal anti-inflammatory drug use.
§Model 2 + BMI.
‖Values are P interaction instead of P trend.
¶Further adjusted for sex.

Table 4. Association of total adiponectin with colorectal adenoma according to tertiles of leptin and TNF-α

Measurement	Tertiles for total adiponectin*			*P* trend†
	Lowest	Middle	Highest	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	
Leptin‡ §				0.007‖
Highest tertile	1.00 (reference)	0.78 (0.52–1.15)	0.70 (0.44–1.09)	0.05
Middle tertile	1.02 (0.68–1.53)	0.85 (0.57–1.28)	0.40 (0.25–0.64)	<0.001
Lowest tertile	0.52 (0.32–0.84)	0.69 (0.43–1.09)	0.71 (0.45–1.10)	0.21
TNF-α§ ¶				0.20‖
Highest tertile	1.00 (reference)	1.03 (0.68–1.58)	0.57 (0.35–0.93)	0.04
Middle tertile	1.33 (0.87–2.02)	1.00 (0.65–1.55)	1.19 (0.76–1.86)	0.96
Lowest tertile	1.24 (0.80–1.93)	1.14 (0.74–1.76)	0.77 (0.49–1.21)	0.01

*Cutoff points were 3.64 and 5.26 μg/mL for men and 5.76 and 8.49 μg/mL for women.
†Statistical tests for trend (two-sided) were assessed by assigning ordinal values to tertiles of each measurement.
‡Cutoff points were 1,756 and 3,842 pg/mL for men and 3,856 and 7,908 pg/mL for women.
§Adjusted for age, screening period, duration of fasting, sex, cigarette smoking, alcohol drinking, family history of colorectal cancer, nonsteroidal anti-inflammatory drug use, and BMI.
‖Values are *P* interaction instead of *P* trend.
¶Cutoff points were 2.38 and 2.97 pg/mL for men and 2.22 and 2.79 pg/mL for women.

adenoma. In this analysis, men and women were combined according to sex-specific tertiles of adiponectin, and stratified by leptin and TNF-α, respectively, based on sex-specific tertiles for controls. We observed a statistically significant interaction of total adiponectin with leptin (*P* interaction = 0.007), but not with TNF-α (*P* interaction = 0.20; Table 4). Compared with those in the lowest tertile of total adiponectin and highest tertile of leptin, those in the lowest tertiles of total adiponectin and leptin showed a statistically significant decrease in OR for colorectal adenoma (OR, 0.52; 95% CI, 0.32–0.84). However, a further decrease in ORs was not seen with increasing levels of total adiponectin among those in the lowest tertile of leptin (*P* trend = 0.21). In contrast, those in the middle and highest tertiles of leptin showed an inverse association between total adiponectin and colorectal adenoma. An inverse association was more prominent among those in the middle tertile of leptin (*P* trend < 0.001), with a significantly reduced OR of colorectal adenoma for the highest tertile of total adiponectin (OR, 0.40; 95% CI, 0.25–0.64). Of note, increasing levels of leptin were associated with elevated ORs of colorectal adenoma only among those in the lowest tertile of total adiponectin (*P* trend = 0.01; data not shown). After adjustment for BMI and other potential confounders, ORs for the lowest, middle, and highest tertiles of leptin were 1.00 (reference), 1.96 (95% CI, 1.21-3.17), and 1.92 (95% CI, 1.19-3.11), respectively, in the lowest tertile of total adiponectin (data not shown). If the above analysis of total adiponectin and leptin was repeated without interaction terms, mutually adjusted ORs of colorectal adenoma for the lowest, middle, and highest tertiles were 1.00 (reference), 0.90 (95% CI, 0.70–1.15), and 0.71 (95% CI, 0.54–0.93), respectively, for total adiponectin, whereas the corresponding values were 1.00 (reference), 1.13 (95% CI, 0.86–1.49), and 1.25 (95% CI, 0.92–1.69), respectively, for leptin (data not shown). In accordance with the above results, we observed a marginally significant interaction of HMW adiponectin with leptin (*P* interaction = 0.07), but not with TNF-α (*P* interaction = 0.21; Table 5). Again, these results were not essentially changed by additional adjustment for indicators of energy balance, dietary factors, and metabolic factors (*P* interaction with leptin = 0.006 and 0.07 for total and HMW adiponectin, respectively; data not shown). Results were essentially the same when the above analysis was conducted for men and women separately (*P* interaction of total adiponectin with leptin = 0.04 and 0.01 for men and women, respectively; data not shown).

Discussion

In this study, we observed an inverse association between total adiponectin and colorectal adenoma with statistical significance. This association remained significant, albeit considerably attenuated, after further adjustment for BMI, a major determinant of insulin resistance (2), suggesting that adiponectin may decrease the risk of colorectal neoplasia through mechanisms other than the indirect mechanism through insulin resistance. We also observed an inverse association of HMW adiponectin with colorectal adenoma, although significance was lost with additional adjustment for BMI. HMW adiponectin has a potent insulin-sensitizing effect, whereas circulating levels of HMW adiponectin and the degree of insulin sensitivity are determined mainly by the amount of adipose tissue (2, 3). Given that improved insulin sensitivity has been related to a decreased risk of