

Supplementary Table 1. Occurrence of *BRAF* mutation among colorectal cancers according to MSI status

	Total N	MSS	MSI-high	P value (chi-square test)
<i>BRAF</i> mutation				<0.0001
(-)	1081 (86%)	988 (92%)	93 (48%)	
(+)	183 (15%)	81 (7.6%)	102 (52%)	

MSI, microsatellite instability; MSS, microsatellite stable.

Supplementary Table 2. Clinical, pathologic or molecular characteristics of colorectal cancer according to CIMP/MSI subtypes

Clinical, pathologic or molecular feature	Total N	CIMP-high MSI-high	CIMP-low/0 MSI-high	CIMP-high MSS	CIMP-low/0 MSS	P value
All cases	1188	141	46	65	936	
Sex						0.0001
Male (HPFS)	520 (44%)	37 (26%)	22 (48%)	28 (43%)	433 (46%)	
Female (NHS)	668 (56%)	104 (74%)	24 (52%)	37 (57%)	503 (54%)	
Mean age ± SD	68.4 ± 8.9	71.5 ± 6.5	66.2 ± 8.6	71.0 ± 8.6	67.7 ± 8.8	<0.0001
Body mass index						0.75
<30 kg/m <sup>2</sup>	963 (82%)	112 (80%)	36 (80%)	56 (86%)	759 (82%)	
≥30 kg/m <sup>2</sup>	216 (18%)	28 (20%)	9 (20%)	9 (14%)	170 (18%)	
Year of diagnosis						0.0026
Prior to 1995	390 (33%)	31 (22%)	12 (26%)	15 (23%)	332 (35%)	
1995 to 2006	798 (67%)	110 (78%)	34 (74%)	50 (77%)	604 (65%)	
No. of first-degree relatives with colorectal cancer						0.0008
0	954 (81%)	109 (78%)	32 (71%)	49 (75%)	764 (82%)	
1	173 (15%)	22 (16%)	5 (11%)	13 (20%)	133 (14%)	
≥2	54 (4.6%)	9 (6.4%)	8 (18%)	3 (4.6%)	34 (3.7%)	
Pre-diagnosis physical activity (MET-hours/week)						0.45
<18	680 (60%)	91 (66%)	28 (67%)	39 (61%)	522 (60%)	
≥18	440 (39%)	47 (34%)	14 (33%)	25 (39%)	354 (40%)	
Pre-diagnosis smoking status						0.16
Never	451 (39%)	43 (31%)	19 (44%)	29 (45%)	360 (39%)	
Former/current smokers	712 (61%)	96 (69%)	24 (56%)	36 (55%)	556 (61%)	

(Supplementary Table 2, continued)

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Clinical, pathologic or molecular feature	Total N	CIMP-high MSI-high	CIMP-low/0 MSI-high	CIMP-high MSS	CIMP-low/0 MSS	P value
Pre-diagnosis alcohol consumption						0.0032
No	389 (33%)	65 (46%)	20 (44%)	18 (28%)	286 (31%)	
<15 g/day	549 (47%)	50 (36%)	21 (47%)	35 (54%)	443 (48%)	
≥15 g/day	238 (20%)	25 (18%)	4 (8.9%)	12 (18%)	197 (21%)	
Disease stage						<0.0001
I	272 (25%)	21 (15%)	15 (37%)	13 (22%)	223 (27%)	
II	336 (31%)	85 (63%)	16 (39%)	11 (18%)	224 (27%)	
III	313 (29%)	23 (17%)	7 (17%)	18 (30%)	265 (32%)	
IV	157 (15%)	7 (5.1%)	3 (7.3%)	18 (30%)	129 (15%)	
Tumor differentiation						<0.0001
Well to moderate	1064 (90%)	87 (62%)	41 (89%)	58 (89%)	878 (95%)	
Poor	117 (9.9%)	54 (38%)	5 (11%)	7 (11%)	51 (5.5%)	
Mucinous component						<0.0001
0%	702 (61%)	44 (32%)	19 (41%)	29 (45%)	610 (68%)	
1-49%	294 (26%)	49 (35%)	18 (39%)	26 (40%)	201 (22%)	
≥50%	155 (13%)	46 (33%)	9 (20%)	10 (15%)	90 (10%)	
Signet ring cell component						<0.0001
0%	1026 (89%)	98 (71%)	39 (85%)	50 (78%)	839 (93%)	
1-49%	104 (9.1%)	34 (25%)	7 (15%)	14 (22%)	49 (5.4%)	
≥50%	19 (1.7%)	6 (4.4%)	0	0	13 (1.4%)	
<i>BRAF</i> mutation						<0.0001
(-)	1005 (85%)	44 (31%)	44 (98%)	34 (52%)	883 (95%)	
(+)	176 (15%)	97 (69%)	1 (2.2%)	31 (48%)	47 (5.1%)	

(Supplementary Table 2, continued)

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Clinical, pathologic or molecular feature	Total N	CIMP-high MSI-high	CIMP-low/0 MSI-high	CIMP-high MSS	CIMP-low/0 MSS	P value
<i>KRAS</i> mutation						<0.0001
(-)	754 (64%)	134 (95%)	27 (61%)	42 (65%)	551 (59%)	
(+)	429 (36%)	7 (5.0%)	17 (39%)	23 (35%)	382 (41%)	
<i>PIK3CA</i> mutation						0.24
(-)	893 (81%)	100 (77%)	33 (83%)	44 (75%)	716 (82%)	
(+)	204 (19%)	30 (23%)	7 (18%)	15 (25%)	152 (18%)	
LINE-1 methylation level (mean $\pm$ SD)						<0.0001
	62.7 $\pm$ 9.5	67.5 $\pm$ 8.5	66.8 $\pm$ 10.1	67.2 $\pm$ 8.5	61.4 $\pm$ 9.4	
<i>ABCBI</i> expression level (Log <sub>2</sub> intensity)						0.0011
Median	6.47	6.41	6.40	6.46	6.50	
(interquartile range)	(6.35-6.81)	(6.33-6.60)	(6.35-6.54)	(6.36-6.64)	(6.36-6.89)	

(%) indicates the proportion of cases with a specific clinical, pathologic or molecular feature among cancers located in each CIMP/MSI subtypes (CIMP-high MSI-high, CIMP-low/0 MSI-high, CIMP-high MSS, CIMP-low/0 MSS). P values were calculated by chi-square test, except for age, LINE-1 (one-way ANOVA test), and ABCB1 (Kruskal-Wallis test). CIMP, CpG island methylator phenotype; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent task; MSI, microsatellite instability; MSS, microsatellite stable; NHS, Nurses' Health Study; SD, standard deviation.