

Table SI. Baseline characteristics of participants in this study.

Characteristic	Non-CRC (n=36,809)	CRC (n=282)	P-value
Smoking			<0.0001
No smoking	6,532 (18.8; 17.7, 19.9)	43 (15.5; 11.2, 20.9)	
Past smoking	9,335 (24.9; 24.2, 25.7)	128 (45.4; 37.7, 53.3)	
Current smoking	7,988 (22.2; 21.4, 23.1)	41 (15.1; 10.7, 20.7)	
Secondhand smoking	12,954 (34.1; 33.2, 34.9)	70 (24.1; 17.2, 32.8)	
Cotinine, ng/ml			0.0260
<0.015	7,676 (23.4; 22.0, 24.8)	67 (29.2; 22.3, 37.3)	
0.015-3	17,876 (48.5; 47.5, 49.5)	139; (51.5; 43.5, 59.5)	
3-10	626 (1.6; 1.5, 1.8)	3 (0.7; 0.2, 2.5)	
≥10	8,987 (26.5; 25.4, 27.5)	44 (18.5; 13.7, 24.6)	
Age started smoking cigarettes regularly, years			0.4124
Never regular	809 (5.15; 4.69, 5.66)	7 (4.79; 1.72, 12.64)	
<20	12,045 (71.95; 71.06, 72.82)	108 (66.81; 58.33, 74.32)	
≥20	4,412 (22.90; 22.13, 23.69)	53 (28.40; 21.45, 36.56)	
Age, years	36,809 (46.8; 46.4, 47.2)	282 (68.3; 66.3, 70.3)	<0.0001
Sex			0.1532
Male	18,550 (49.4; 48.9, 49.9)	146 (44.4; 37.7, 51.4)	
Female	18,259 (50.6; 50.1, 51.1)	136 (55.6; 48.6, 62.3)	
Ethnicity			<0.0001
Mexican-American	6,341 (7.6; 6.5, 8.7)	15 (1.3; 0.6, 2.7)	
Non-Hispanic White	17,351 (70.9; 68.7, 73.0)	192 (84.4; 79.9, 88.1)	
Non-Hispanic Black	7,500 (10.5; 9.4, 11.8)	56 (9.5; 7.1, 12.7)	
Other Hispanic	2,844 (5.1; 4.3, 6.1)	13 (2.5; 1.2, 5.3)	
Other ethnicities	2,773 (5.9; 5.4, 6.5)	6 (2.2; 0.6, 7.4)	
Education			0.0972
Less than high school	9,710 (16.9; 15.9, 17.9)	89 (21.6; 16.7, 27.3)	
High school grad/GED or equivalent	8,557 (23.7; 22.8, 24.6)	63 (19.2; 14.1, 25.7)	
More than high school	18,542 (59.4; 57.8, 60.9)	130 (59.2; 51.7, 66.3)	
Marital status			0.1020
Married/living with partner	22,211 (64.1; 63.0, 65.2)	149 (58.9; 52.2, 65.3)	
Widowed/divorced/separated/never married	14,598 (35.9; 34.8, 37.0)	133 (41.1; 34.7, 47.8)	
RIP			0.0032
0-1.00	7,466 (13.9; 13.0, 14.8)	50 (13.7; 9.8, 18.9)	
1.01-3.00	15,427 (36.0; 34.9, 37.1)	142 (46.8; 39.5, 54.2)	

>3.00	13,916 (50.1; 48.4, 51.7)	90 (39.5; 32.3, 47.1)	
Alcohol consumption			0.9949
No	5,225 (11.3; 10.4, 12.3)	35 (11.4; 7.5, 16.9)	
Yes	31,584 (88.7; 87.7, 89.6)	247 (88.6; 83.1, 92.5)	
BMI, kg/m ²			0.1807
<18.50	565 (1.6; 1.5, 1.8)	2 (0.2; 0.0, 0.8)	
18.50-24.99	10,450 (30.0; 29.2, 30.9)	66 (26.7; 20.9, 33.5)	
25.00-29.99	12,479 (33.4; 32.7, 34.1)	109 (35.6; 28.4, 43.4)	
≥30.00	13,315 (34.9; 34.1, 35.8)	105 (37.6; 30.6, 45.1)	

Continuous data are presented as the number of individuals (survey-weighted mean; 95% CI), and the P-values were determined by survey-weighted linear regression. Categorical data are presented as the number of individuals (survey-weighted percentage; 95% CI), and the P-value were determined by survey-weighted χ^2 test. BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; GED, General Educational Development; RIP, ratio of family income to poverty.

Table SII. Details of the GWAS data analyzed in the Mendelian randomization.

A, Finngen (C3_COLORECTAL_EXALLC) data						
Phenotype	Sample size	No. of SNPs	R ²	Cochran's Q test	MR PRES SO	Pleiotropy
Colorectal cancer	293,646	-	-	-	-	-
B Meta-analysis data						
Phenotype	Sample size	No. of SNPs	R ²	Cochran's Q test	MR PRES SO	Pleiotropy
Age of initiation of regular smoking	341,427	8	0.12 %	0.368	0.513	0.771
Cigarettes per day	337,334	52	1.41 %	0.982	0.977	0.676
Smoking cessation	547,219	21	0.93 %	0.663	0.668	0.711
Smoking initiation	1,232,091	331	5.10 %	0.088	0.104	0.289
C, ukb-b-7460 data (IEU database)						
Phenotype	Sample size	No. of SNPs	R ²	Cochran's Q test	MR PRES SO	Pleiotropy
Pack years of adult smoking as a proportion of life span exposed to smoking	142,387	13	0.59 %	0.831	0.868	0.607

GWAS, genome-wide association studies; SNP, single-nucleotide polymorphisms.

Table SIII. Target sequences of shRNAs and siRNAs.

Name	Target sequence
shCKAP2L #1	5'-CCACCTTCTAAATCTACTATT-3'
shCKAP2L #2	5'-GCAGCAGTTAACAGATCAAGG-3'
shCKAP2L #3	5'-GCAGATTTAATTCAGCCATTC-3'
shCKAP2L #4	5'-CTATATGAAGAGGCCATTAAA-3'
shNC	5'-GCTTCGCGCCGTAGTCTTA-3'
siAREG	Sense: 5'-CUUCGACAAGAGAAUGGAA-3' Antisense: 5'-UCCAUCUCUUGUCGAAG-3'
siNC	Sense: 5'-UUCUCCGAACGUGUCACGU-3'
siNC	Antisense: 5'-ACGUGACACGUUCGGAGAA-3'

AREG, amphiregulin; CKAP2L, cytoskeleton-associated protein 2-like; NC, negative control; shRNA, short hairpin RNA; siRNA, small interfering RNA.

Table SIV. Primer sequences used for reverse transcription-quantitative PCR.

Primer	Sequence, 5'-3'
CKAP2L	F: ACAGAACCACAGAAGGGATTACT
	R: CACTTCCGGCATCCCATTATTC
β -actin	F: CCTTCCTGGGCATGGAGTC
	R: TGATCTTCATTGTGCTGGGTG
AREG	F: CTGCCTTTATGTCTGCTGTGATC
	R: CGTTCCTCAGCTTCTCCTTCATA
ChIP (AREG)	F: TGTGCGAACGTCTGTAGGG
	R: GTTTAAGTTCCACTTCTCTCAGC

AREG, amphiregulin; ChIP, chromatin immunoprecipitation; CKAP2L, cytoskeleton-associated protein 2-like; F, forward; R, reverse.

Table SV. Primary antibodies used for western blotting.

Antibody	Cat. no.	Dilution	Supplier
Anti-CKAP2L	17143-1-AP	1:1,000	Proteintech Group, Inc.
Anti-p-STAT3	ET1607-39	1:1,000	HUABIO
Anti-EGFR	T55112	1:5,000	Abmart Pharmaceutical Technology Co., Ltd.
Anti-p-EGFR	T55232	1:500	Abmart Pharmaceutical Technology Co., Ltd.
Anti-cyclin A2	ET1612-26	1:1,000	HUABIO
Anti-cyclin B1	ET1608-27	1:5,000	HUABIO
Anti-cyclin D1	ET1601-31	1:5,000	HUABIO
Anti-CDK1	ET1607-51	1:1,000	HUABIO
Anti-CDK2	ET1602-6	1:1,000	HUABIO
Anti-E-cadherin	ET1607-75	1:5,000	HUABIO
Anti-N-cadherin	ET1607-37	1:2,000	HUABIO
Anti-Vimentin	ET1610-39	1:20,000	HUABIO
Anti-STAT3	60199-1-Ig	1:300	Proteintech Group, Inc.
Anti- β -actin	20536-1-AP	1:5,000	Proteintech Group, Inc.

CKAP2L, cytoskeleton-associated protein 2-like; EGFR, epidermal growth factor receptor; p-, phosphorylated; STAT3, signal transducer and activator of transcription 3.