

Supplementary material

Table S1. Sample size from individual institute.

No.	Site	Sample	Subset	No.	Site	Sample	Subset
1	PLCO	1951	2	15	NELCS	299	3
2	RUSSIAN_CE	2009	3	16	NIJMEGEN	755	2
3	ISRAEL	1044	2	17	TAMPA	146	2
4	TORONTO	1022	1	18	VANDERBILT	1048	2
5	EAGLE	3195	3	19	MDCS	239	3
6	MDACC	1750	1	20	NSHDC	402	3
7	ATBC_1	257	1	21	TCC	362	2
8	ATBC_2	935	1	22	COPENHAGEN	1691	1
9	CANADA	585	2	23	FIELD_2008	183	2
10	CAPUA	1220	1	24	FIELD_2013	636	2
11	FHCRC	298	2	25	GER-1680	779	2
12	HSPH	2607	1	26	IARC	1904	3
13	KENTUCKY	207	2	27	NORWAY	719	3
14	MEC	406	2	28	RESOLUCENT	659	2

“Site” indicates the code for the institute; “Sample” indicates the number of individuals from the site; and “Subset” indicates which subset (1-3) those samples were grouped. 1, PLCO= The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, National Cancer Institute (US); 2, RUSSIAN_CE= The IARC L2 Study, International Agency for Research on Cancer-; 3, ISRAEL=Technion Institute; 4, Toronto=Samuel Lunenfeld Research Institute and Princess Margaret Hospital; 5, EAGLE=National Cancer Institute – Environment and Genetics in Lung Cancer Etiology; 6, MDACC=MD Anderson Cancer Center; 7-8, ATBC=National Cancer Institute - Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study ; 9, CANADA=University of British Columbia - Early Detection of Lung Cancer Study ; 10, CAPUA= Cancer de Pulmon en Asturias, University of Oviedo and CIBERESP; 11, FHCRC= The Carotene and Retinol Efficacy Trial , Fred Hutchinson Cancer Research Center; 12, HSPH=Harvard Lung Cancer Study, Harvard School of Public Health; 13, KENTUCKY=University of Kentucky; 14, MEC=Multi-ethnic cohort study, University of Hawaii and University of Southern California; 15, NELCS=New England Lung Cancer Study, Dartmouth College; 16, NIJMEGEN=Nijmegen Lung Cancer Study, Radboud University Medical Center; 17, TAMPA=Tampa case control study, Washington State University; 18, VANDERBILT=BioVu-Vanderbilt University; 19, MDCS= The Malmö Diet and Cancer Study, Lund University Sweden; 20, NSHDC= Northern Sweden Health and Disease Study, Umea University Sweden; 21, TCC=Total Cancer Care - Moffitt Cancer Center; 22, COPENHAGEN=Copenhagen; 23-24, LLP=Liverpool Lung Cancer Project, University of Liverpool; 25, GER-1680=Germany; 26, IARC= Study European Prospective Investigation into Cancer and Nutrition -- International Agency for Research on Cancer; 27, Norway=The Norway Lung Cancer Study - National Institute of Occupational Health Norway; 28, RESOLUCENT= Resource for the Study of Lung Cancer Epidemiology in North Trent, University of Sheffield.

Table S2. Number of significant SNPs at each step in the analysis and theoretical Bonferroni p value in the analysis.

Histology	Discovery stage							Replication stage
	Step 1 test ¹	Bonferroni P value ²	Step 2 test ³					Validation
			Sub 1	Sub 2	Sub 3	Common	Combined	
NSCLC	1379	3.63x10 ⁻⁵	438	766	925	105	52	2/35
ADE	867	5.77x10 ⁻⁵	356	462	571	108	41	0/26
SQC	468	1.07x10 ⁻⁴	51	80	89	46	10	1/1

1, SNPs with case-only p value less than 0.001 using all the patients in discovery data were selected. 2, Bonferroni P values were calculated by dividing 0.05 by the number of selected SNPs from step 1 tests. For consistency, we used 3.5x10⁻⁵ as the cutoff p value for all the subtype studies. 3, SNPs were chosen based on two criteria: 1), case-control p value < 0.1 from each of the Sub1-3 subset in discovery data and 2), case-control p value < 3.5x10⁻⁵ in the test using the combined discovery data. Sub1-3 indicate the number of SNPs with p value < 0.1 from each subset; "Common" indicates the number of SNPs common to all the three subsets; "Combined" indicates the number of SNPs from "Common" that have a case-control p value < 3.5x10⁻⁵ in the combined data analysis in discovery stage; "Validation" indicates the number of SNPs available in replication genotype data and the number of SNPs validated in replication stage with case-control p value less than 0.05. We also replicated the signals at one SNP from ADE and two SNPs from SQC subgroup using imputed replication data.

Table S3. Significant SNPs at step 2 test in discovery stage from NSCLC, ADE and SQC cohorts and their interaction p values in replication study.

SNP	CHR	Pos	P_S1	P_S2	P_S3	P_combined	P_main	P_replica
NSCLC								
rs1166706	1	78359029	1.24X10-3	1.41X10-2	3.23X10-2	4.37X10-6	5.59X10-1	2.95X10-1
rs4839580	1	111430758	1.25X10-2	5.04X10-2	1.96X10-3	1.14X10-5	2.74X10-1	7.97X10-1
rs7540041	1	203769532	5.10X10-2	5.96X10-4	9.27X10-2	2.33X10-5	8.06X10-2	4.90X10-1
rs4951259	1	203785169	5.51X10-2	5.44X10-4	9.50X10-2	2.45X10-5	8.07X10-2	5.67X10-1
rs7552670	1	203768328	5.07X10-2	7.51X10-4	9.32X10-2	2.80X10-5	7.96X10-2	4.90X10-1
rs7546400	1	203777799	6.04X10-2	5.39X10-4	9.67X10-2	2.85X10-5	8.82X10-2	5.09X10-1
rs10494844	1	203769891	5.23X10-2	7.45X10-4	9.53X10-2	3.00X10-5	7.90X10-2	5.17X10-1
rs6441286	3	159728878	3.39X10-3	1.67X10-2	4.79X10-3	1.16X10-5	6.60X10-1	2.02X10-2
rs693476	3	128743450	4.78X10-2	7.37X10-3	4.77X10-3	1.55X10-5	4.96X10-1	1.79X10-1
rs11727860	4	182179570	6.25X10-3	9.89X10-3	1.50X10-3	9.62X10-7	8.90X10-1	9.57X10-1
rs10947963	6	41305976	2.89X10-2	4.66X10-2	4.57X10-3	1.74X10-5	7.71X10-1	4.18X10-1
rs144936251	6	170401481	6.14X10-2	4.98X10-3	5.64X10-2	2.84X10-5	9.55X10-1	NA
rs17723637	9	109687403	7.95X10-3	1.33X10-2	4.14X10-3	1.06X10-5	2.89X10-1	9.76X10-3

Commented [CIA1]: This title is confusing because you also included the validation result. Did you perform a meta-analysis? If so add that as the final column. Also in the text you said these results included imputed data. Please add a column indicating which snp was directly genotyped and which was imputed, or maybe you could just put a star on the genotyped SNPs.

Commented [YL2R1]: The title was changed. The signals from imputed SNPs are labeled with star in the table

rs12294383	11	129239091	4.33X10-2	2.89X10-3	3.03X10-2	4.94X10-6	4.23X10-1	1.92X10-1
rs17484524	15	78772676	5.63X10-7	3.91X10-5	1.20X10-3	3.01X10-13	4.26X10-37	8.77X10-4
rs2656065	15	78750549	4.80X10-7	3.14X10-5	1.54X10-3	3.62X10-13	3.48X10-36	2.16X10-3
rs2656065	15	78750549	5.76X10-7	3.02X10-5	1.49X10-3	3.87X10-13	3.58X10-36	2.16X10-3
rs9788721	15	78802869	1.41X10-7	2.23X10-4	8.55X10-4	4.56X10-13	2.29X10-48	1.39X10-2
rs17405217	15	78731149	9.75X10-7	3.64X10-5	1.21X10-3	4.62X10-13	4.90X10-37	1.61X10-3
rs2656052	15	78740932	1.15X10-6	1.99X10-5	1.76X10-3	5.07X10-13	1.33X10-36	1.76X10-3
rs17483548	15	78730313	1.11X10-6	2.83X10-5	1.72X10-3	6.29X10-13	5.60X10-37	2.71X10-3
rs10519203	15	78814046	1.20X10-7	5.85X10-4	9.01X10-4	6.95X10-13	6.22X10-49	1.83X10-3
rs931794	15	78826180	9.61X10-8	5.61X10-4	1.03X10-3	7.97X10-13	8.41X10-51	8.53X10-4
rs4887056	15	78734585	9.32X10-7	3.39X10-5	2.49X10-3	1.02X10-12	3.52X10-36	NA
rs17483721	15	78733731	6.17X10-7	3.48X10-5	3.08X10-3	1.09X10-12	5.39X10-37	2.02X10-3
rs2009746	15	78754102	7.78X10-7	4.25X10-5	2.58X10-3	1.20X10-12	1.58X10-36	1.99X10-3
rs8040868	15	76698236	8.39X10-7	2.07X10-5	8.92X10-3	1.37X10-12	1.51X10-46	8.05X10-3
rs17483929	15	78742376	7.78X10-7	5.11X10-5	2.82X10-3	1.77X10-12	1.19X10-37	1.77X10-3
rs8034191	15	78806023	3.19X10-7	8.02X10-4	1.62X10-3	3.86X10-12	9.26X10-48	4.89X10-3
rs12914385	15	78898723	1.89X10-6	6.36X10-5	5.47X10-3	4.04X10-12	1.37X10-48	3.84X10-3
rs2036527	15	78851615	6.94X10-7	1.86X10-4	5.10X10-3	6.63X10-12	7.68X10-53	4.14X10-3
rs55781567	15	78857986	1.40X10-6	2.38X10-4	5.49X10-3	1.65X10-11	3.97X10-53	NA
rs1317286	15	78896129	1.13X10-6	2.02X10-3	4.19X10-3	9.65X10-11	6.92X10-50	2.70X10-3
rs1051730	15	78894339	7.40X10-7	2.13X10-3	6.40X10-3	9.85X10-11	9.25X10-51	5.95X10-3
rs16969968	15	78882925	1.18X10-6	1.65X10-3	6.21X10-3	1.02X10-10	5.38X10-51	7.38X10-3
rs951266	15	78878541	7.82X10-7	2.14X10-3	6.14X10-3	1.15X10-10	2.04X10-51	5.05X10-3
rs10851907	15	78915864	4.10X10-5	1.54X10-4	1.15X10-2	1.78X10-10	5.34X10-42	3.97X10-3
rs17487223	15	78923987	7.27X10-5	2.49X10-3	5.05X10-3	2.14X10-9	4.89X10-43	9.85X10-3
rs56117933	15	78832349	1.17X10-3	1.76X10-3	1.21X10-3	4.71X10-9	6.25X10-29	1.08X10-2
rs17487514	15	78953785	1.20X10-2	3.96X10-3	2.94X10-3	4.51X10-7	6.82X10-20	5.80X10-3
rs7163730	15	78814681	5.32X10-2	1.98X10-2	1.08X10-3	8.78X10-6	5.66X10-32	3.17X10-3
rs17235533	15	33356782	4.73X10-2	5.03X10-2	2.17X10-4	1.57X10-5	7.06X10-1	4.54X10-2
rs1996371	15	78956806	1.91X10-3	9.18X10-2	2.79X10-2	1.68X10-5	6.50X10-26	1.69X10-2
rs77438700	15	78906637	1.42X10-3	4.34X10-2	4.64X10-2	1.78X10-5	1.13X10-8	6.76X10-2
rs10519781	15	33362794	9.44X10-2	6.69X10-2	4.47X10-5	1.87X10-5	2.06X10-1	1.30X10-1
rs11638372	15	78983559	2.08X10-3	9.24X10-2	3.57X10-2	1.95X10-5	5.24X10-25	8.98X10-2
rs4887053	15	78712699	6.91X10-2	2.72X10-2	1.78X10-3	3.00X10-5	1.10X10-22	1.59X10-4
rs299744	18	46193230	8.21X10-2	3.56X10-4	1.90X10-3	1.33X10-6	6.78X10-1	5.88X10-1
rs2624160	18	46192191	7.87X10-2	2.76X10-3	5.72X10-3	1.08X10-5	4.88X10-1	7.29X10-1

rs299716	18	46162410	2.84X10-2	2.55X10-3	2.23X10-2	2.13X10-5	7.62X10-1	5.93X10-1
rs299729	18	46170624	7.41X10-2	2.48X10-3	1.22X10-2	2.50X10-5	7.68X10-1	7.03X10-1
rs177259	18	46164961	4.93X10-2	1.05X10-2	8.51X10-3	2.82X10-5	6.71X10-1	5.97X10-1
Adenocarcinoma								
rs7540041	1	203769532	2.73X10-2	1.44X10-3	1.21X10-2	4.32X10-6	3.12X10-2	9.90X10-1
rs7552670	1	203768328	2.77X10-2	1.47X10-3	1.24X10-2	4.55X10-6	3.38X10-2	9.90X10-1
rs10494844	1	203769891	2.85X10-2	1.45X10-3	1.27X10-2	4.83X10-6	3.32X10-2	9.80X10-1
rs4951259	1	203785169	3.11X10-2	1.46X10-3	1.30X10-2	5.37X10-6	3.55X10-2	9.32X10-1
rs7546400	1	203777799	3.41X10-2	1.38X10-3	1.34X10-2	6.02X10-6	3.88X10-2	9.98X10-1
rs6685918	1	203777309	4.84X10-2	1.28X10-3	1.36X10-2	7.60X10-6	5.21X10-2	9.95X10-1
rs11727860	4	182179570	6.52X10-3	5.60X10-2	5.29X10-4	1.67X10-6	3.08X10-1	8.11X10-1
rs6810985	4	25765527	1.56X10-3	6.82X10-2	1.63X10-2	8.04X10-6	3.31X10-1	6.09X10-1
rs10477550	5	115429757	9.05X10-2	7.69X10-4	4.30X10-2	1.95X10-5	3.57X10-3	4.33X10-3*
rs11781075	8	31272835	8.22X10-3	5.69X10-2	2.49X10-3	2.80X10-5	5.89X10-1	1.55X10-1
rs10815428	9	6400030	1.20X10-2	2.98X10-2	2.69X10-2	1.66X10-5	7.09X10-2	5.63X10-2
rs12294383	11	129239091	6.93X10-2	2.63X10-3	2.56X10-2	9.76X10-6	8.35X10-1	8.38X10-2
rs9569039	13	55044198	4.98X10-3	4.54X10-2	1.80X10-3	2.21X10-5	8.13X10-1	2.99X10-1
rs2057133	14	63726382	6.25X10-3	5.10X10-2	7.97X10-3	1.14X10-5	1.82X10-3	2.16X10-1
rs9788721	15	78802869	1.04X10-8	5.27X10-3	4.19X10-4	3.35X10-12	2.52X10-24	5.43X10-3
rs10519203	15	78814046	1.65X10-8	9.79X10-3	9.59X10-4	1.61X10-11	4.69X10-24	2.81X10-3
rs17484524	15	78772676	1.05X10-7	3.46X10-3	1.16X10-3	1.95X10-11	8.55X10-18	8.17X10-4
rs931794	15	78826180	1.05X10-8	1.04X10-2	1.45X10-3	2.28X10-11	3.58X10-25	1.90X10-3
rs17405217	15	78731149	1.53X10-7	3.11X10-3	1.16X10-3	2.35X10-11	5.64X10-18	2.08X10-3
rs2656065	15	78750549	1.12X10-7	3.28X10-3	1.32X10-3	2.75X10-11	6.69X10-18	2.70X10-3
rs2656052	15	78740932	1.87X10-7	2.21X10-3	1.56X10-3	2.85X10-11	4.80X10-18	1.95X10-3
rs2656065	15	78750549	1.35X10-7	3.34X10-3	1.28X10-3	3.11X10-11	6.65X10-18	2.70X10-3
rs17483548	15	78730313	1.80X10-7	2.54X10-3	1.77X10-3	3.25X10-11	7.43X10-18	3.61X10-3
rs2009746	15	78754102	1.63X10-7	3.44X10-3	2.30X10-3	6.28X10-11	4.91X10-18	2.47X10-3
rs4887056	15	78734585	3.22X10-7	2.54X10-3	2.37X10-3	7.49X10-11	8.39X10-18	NA
rs17483721	15	78733731	1.99X10-7	2.80X10-3	2.80X10-3	7.64X10-11	3.45X10-18	2.62X10-3
rs8034191	15	78806023	3.71X10-8	1.30X10-2	1.96X10-3	7.90X10-11	1.71X10-23	4.89X10-3
rs17483929	15	78742376	1.62X10-7	4.06X10-3	2.58X10-3	9.78X10-11	1.52X10-18	2.46X10-3
rs2036527	15	78851615	9.69X10-8	4.77X10-3	4.95X10-3	1.52X10-10	1.52X10-26	4.33X10-3
rs55781567	15	78857986	1.70X10-7	6.19X10-3	4.96X10-3	3.14X10-10	4.68X10-27	8.45X10-3
rs8040868	15	76698236	4.69X10-7	4.53X10-3	1.19X10-2	5.50X10-10	1.16X10-21	1.95X10-2
rs1317286	15	78896129	8.93X10-8	3.10X10-2	2.29X10-3	6.18X10-10	7.07X10-26	8.06X10-3

rs12914385	15	78898723	3.02X10-7	8.39X10-3	9.64X10-3	7.54X10-10	1.15X10-24	1.20X10-2
rs16969968	15	78882925	1.17X10-7	2.42X10-2	4.88X10-3	1.15X10-9	2.64X10-26	5.57X10-3
rs1051730	15	78894339	8.81X10-8	3.18X10-2	4.76X10-3	1.32X10-9	2.56X10-26	9.27X10-3
rs951266	15	78878541	9.37X10-8	3.32X10-2	6.93X10-3	2.55X10-9	1.34X10-26	1.38X10-2
rs17487223	15	78923987	1.47X10-5	1.43X10-2	4.28X10-3	8.66X10-9	2.11X10-23	4.80X10-3
rs10851907	15	78915864	2.22X10-5	1.22X10-2	1.10X10-2	1.44X10-8	1.99X10-21	1.55X10-2
rs13180	15	78789488	9.14X10-2	4.67X10-4	8.10X10-3	1.97X10-6	1.51X10-11	5.22X10-4
rs74386627	15	78908077	1.38X10-2	2.45X10-2	4.97X10-2	2.77X10-5	2.64X10-3	NA
rs184039141	18	53068769	1.68X10-3	1.98X10-2	4.36X10-2	3.18X10-6	1.21X10-1	8.21X10-1
Squamous cell carcinoma								
rs4657670	1	167534270	5.33X10-2	2.68X10-5	3.70X10-2	7.11X10-7	9.38X10-2	5.58X10-1
rs192884100	1	161565856	6.30X10-2	4.81X10-4	7.49X10-2	4.23X10-6	4.34X10-2	7.06X10-1
rs3970313	4	185520068	3.26X10-2	6.95X10-3	3.80X10-3	1.31X10-5	1.74X10-1	2.03X10-1
rs75288301	4	160905823	9.12X10-2	6.08X10-2	1.04X10-4	2.46X10-5	6.67X10-1	3.55X10-1
rs73275922	5	120653176	1.30X10-2	3.76X10-2	2.21X10-3	2.26X10-5	1.16X10-1	8.77X10-1
rs4557740	8	18015120	1.54X10-3	3.29X10-2	3.09X10-3	1.13X10-5	6.51X10-1	3.27X10-3*
rs4751674	10	116139029	6.34X10-2	2.70X10-4	9.10X10-2	1.07X10-5	9.39X10-1	2.62X10-2
c12_pos28182123	12	28182123	5.19X10-2	1.76X10-2	5.48X10-3	2.64X10-5	4.69X10-2	NA
rs6573400	14	62239572	3.48X10-3	2.14X10-2	2.59X10-2	2.03X10-5	9.18X10-1	2.77X10-1
rs11544453	22	46316863	5.61X10-4	7.07X10-2	2.17X10-3	8.84X10-6	9.30X10-1	4.05X10-2*

P_S1, P_S2 and P_S3 indicate the case-control p values from each of the subset at discovery stage; P_combined indicates the case-control p value from combined data analysis in discovery stage; P_main indicates the p values from disease and SNP association when no gene-smoking interaction is considered in the combined discovery data; P_replica indicates the case-control p values from replication data including imputed SNPs. In step 2 test, significant SNPs were chosen based on two criteria: 1, p value < 0.1 from each of the S1-S3 subset in discovery data and 2, p value < 3.5x10-5 in the test using all the discovery data. The significant SNPs with case-control p values < 0.05 were highlighted in the replication analysis and the * indicates the significant signal from imputed replication data. "NA" indicates the SNP was not available in the imputed replication data.

Table S4. Interaction analysis using imputed SNPs from discovery data around the three validated genotyped SNPs.

Chr	SNP	Position	beta	sd	Statistics	P	Genotype
3	rs9824967	159722333	-0.22	0.05	-4.30	1.71X10-5	imputed
3	rs4679868	159724154	-0.22	0.05	-4.45	8.43X10-6	imputed
3	rs10433458	159726252	-0.22	0.05	-4.44	8.87X10-6	imputed
3	rs71147308	159726755	-0.22	0.05	-4.26	2.05X10-5	imputed
3	rs6441286	159728878	-0.22	0.05	-4.42	9.74X10-6	genotyped
3	rs9877910	159730819	-0.22	0.05	-4.46	8.19X10-6	imputed
3	rs66785795	159735441	-0.23	0.05	-4.48	7.63X10-6	imputed

Commented [CIA3]: This is confusing because it does not say if the results are from just the discovery or also the validation set? If they include the validation data you should present results for the discovery and validation stages then the meta-analysis.

Commented [YL4R3]: I inserted "discovery data" in the title

3	rs13096549	159742913	-0.22	0.05	-4.28	1.90X10-5	imputed
3	rs2279741	159744261	-0.22	0.05	-4.46	8.07X10-6	imputed
9	rs10978672	109682501	-0.31	0.07	-4.38	1.18X10-5	imputed
9	rs10978673	109682871	-0.32	0.07	-4.42	9.80X10-6	imputed
9	rs10978675	109683216	-0.31	0.07	-4.39	1.13X10-5	imputed
9	rs10978676	109685081	-0.32	0.07	-4.43	9.64X10-6	imputed
9	rs10978677	109685461	-0.31	0.07	-4.34	1.44X10-5	imputed
9	rs17723637	109687403	-0.32	0.07	-4.43	9.44X10-6	genotyped
9	rs3814541	109689752	-0.32	0.07	-4.44	8.84X10-6	imputed
10	rs539668	116128478	-0.58	0.13	4.55	5.32X10-6	imputed
10	rs1248221	116129222	-0.57	0.13	4.46	8.06X10-6	imputed
10	rs11357629	116129353	-0.55	0.13	4.34	1.44X10-5	imputed
10	rs9420152	116129370	-0.57	0.13	4.50	6.71X10-6	imputed
10	rs1248222	116129432	-0.58	0.13	4.56	5.20X10-6	imputed
10	rs2244178	116131214	-0.57	0.13	4.57	4.88X10-6	genotyped
10	rs541241	116131425	-0.56	0.13	4.48	7.58X10-6	imputed
10	rs610315	116131915	-0.56	0.13	4.45	8.79X10-6	imputed
10	rs75543623	116135688	-0.59	0.13	4.65	3.37X10-6	imputed
10	rs2483911	116136862	-0.59	0.13	4.68	2.87X10-6	imputed
10	rs35288351	116138971	-0.51	0.12	-4.16	3.19X10-5	imputed
10	rs4751674	116139029	-0.52	0.12	-4.28	1.83X10-5	genotyped
10	rs7896317	116139551	-0.57	0.12	-4.59	4.33X10-6	imputed
10	rs7911173	116139682	-0.53	0.12	-4.25	2.17X10-5	imputed
10	rs2093370	116140961	-0.60	0.13	-4.56	5.03X10-6	imputed
10	rs630668	116141185	-0.60	0.13	4.58	4.68X10-6	imputed

The highlighted SNPs indicate the three validated SNPs from genotype interaction analysis.

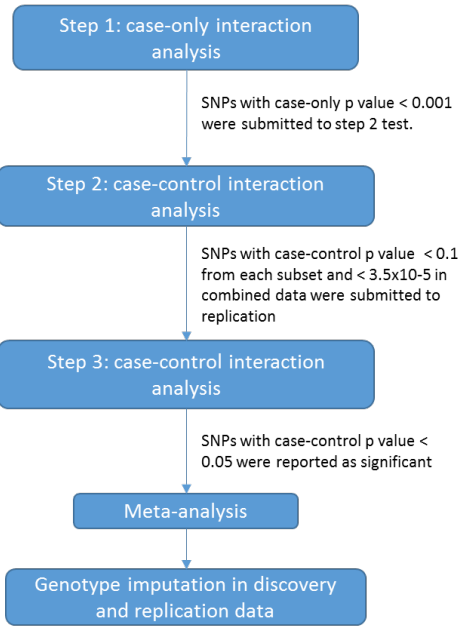
Table S5. Genotype distribution in Never- vs ever-smoker group at the three novel SNPs.

		Cases					Controls				
		Never-smoker	Ever-smoker	Ever-smoker %	OR	P value	Never-smoker	Ever-smoker	Ever-smoker %	OR	P value
rs6441286	AA	545	4100	88.27	1		1531	3398	68.94	1	
	AC	659	5779	89.76	0.86	1.36x10 ⁻²	2205	4512	67.17	1.08	4.58x10 ⁻²
	CC	193	2036	91.34	0.71	1.37x10 ⁻⁴	748	1550	67.45	1.07	2.14x10 ⁻²

	AC+CC	852	7815		0.82	7.14×10^{-4}	2953	6062		1.08	4.23×10^{-2}
	Trend					6.23×10^{-5}					9.99×10^{-2}
rs17723637	AA	1065	8564	88.94	1		3177	6857	68.33	1	
	AG	316	3126	90.82	0.81	2.31×10^{-3}	1188	2408	66.96	1.06	1.35×10^{-1}
	GG	18	243	93.10	0.60	4.29×10^{-2}	125	211	62.80	1.29	3.71×10^{-2}
	AG+GG	334	3369		0.80	6.45×10^{-4}	1313	2619		1.08	5.13×10^{-2}
	Trend					2.84×10^{-4}					1.94×10^{-2}
rs4751674	GG	58	2371	97.61	1		2393	5055	67.87	1	
	AG	81	1679	95.40	1.97	1.12×10^{-4}	1767	3713	67.76	1.01	9.05×10^{-1}
	AA	20	319	94.10	2.56	4.92×10^{-4}	330	710	68.27	0.98	8.24×10^{-1}
	AG+AA	101	1998		2.07	1.44×10^{-5}	2097	4423		1.00	9.81×10^{-1}
	Trend					5.97×10^{-6}					9.28×10^{-1}

Common allele homozygous genotype is used as reference group. chi-square test was conducted to compare the genotype distribution between never- and ever-smoker groups in cases and controls, respectively. Trend test was used to test the proportion of ever-smokers across three genotypes at each SNP.

Discovery stage (three subsets with a total of 13970 controls and 13336 cases):



Replication stage (5377 controls and 3054 cases):

Figure S1. Study scheme in the genome-wide interaction analysis. This flowchart takes the interaction analysis in NSCLC as an example and the sample size varies in adenocarcinoma and squamous cell carcinoma interaction study. Imputation analysis in discovery data was conducted to increase the SNP density around the significant SNPs identified in discovery data; imputation analysis in replication data was conducted to increase the SNP overlap between discovery and replication data.

Commented [CIA5]: You may need to revise this flow chart to show the imputation in the replication data. Also, the first word on the right hand side should be discovery (not discover)