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 EfficacyTrial , 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, Radbound 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.

|  |  |  |
| --- | --- | --- |
|  | Discovery stage | Replication stage |
| Histology | Step 1 test1 | Bonferroni P value2  | Step 2 test3 |  |
|  |  |  | Sub 1 | Sub 2 | Sub 3 | Common  | Combined | Validation |
| 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 diving 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** |
| 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 |
| 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 | 7.14x10-4 | 2953 | 6062 |  | 1.08 | 4.23x10-2 |
|  | Trend |  |  |  |  | 6.23x10-5 |  |  |  |  | 9.99x10-2 |
| rs17723637 | AA | 1065 | 8564 | 88.94 | 1 |  | 3177 | 6857 | 68.33 | 1 |  |
|  | AG | 316 | 3126 | 90.82 | 0.81 | 2.31x10-3 | 1188 | 2408 | 66.96 | 1.06 | 1.35x10-1 |
|  | GG | 18 | 243 | 93.10 | 0.60 | 4.29x10-2 | 125 | 211 | 62.80 | 1.29 | 3.71x10-2 |
|  | AG+GG | 334 | 3369 |  | 0.80 | 6.45x10-4 | 1313 | 2619 |  | 1.08 | 5.13x10-2 |
|  | Trend  |  |  |  |  | 2.84x10-4 |  |  |  |  | 1.94x10-2 |
| rs4751674 | GG | 58 | 2371 | 97.61 | 1 |  | 2393 | 5055 | 67.87 | 1 |  |
|  | AG | 81 | 1679 | 95.40 | 1.97 | 1.12x10-4 | 1767 | 3713 | 67.76 | 1.01 | 9.05x10-1 |
|  | AA | 20 | 319 | 94.10 | 2.56 | 4.92x10-4 | 330 | 710 | 68.27 | 0.98 | 8.24x10-1 |
|  | AG+AA | 101 | 1998 |  | 2.07 | 1.44x10-5 | 2097 | 4423 |  | 1.00 | 9.81x10-1 |
|  | Trend  |  |  |  |  | 5.97x10-6 |  |  |  |  | 9.28x10-1 |

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.



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.