Supplementary Table 1. Comparison of the characteristics between the PLCO and Harvard study

Characteristics	PLCO		HLCS		*P* *
	Frequency	Deaths (%)	Frequency	Deaths (%)	
Total	1,185	798 (67.3)	984	665 (67.5)	
Median overall survival (months)	23.8		39.9		
Age					
≤71	636	400 (62.9)	654	428 (65.4)	<0.0001
>71	549	398 (72.5)	330	237 (71.8)	
Sex					
Male	698	507 (72.6)	507	379 (74.7)	0.0006
Female	487	291 (59.8)	477	286 (59.9)	
Smoking status					
Never	115	63 (54.8)	92	52 (56.5)	0.166
Current	423	272 (64.3)	390	266 (68.2)	
Former	647	463 (71.6)	502	347 (69.1)	
Histology					
Adenocarcinoma	577	348 (60.3)	597	378 (63.3)	<0.0001
Squamous cell carcinoma	285	192 (67.4)	216	156 (72.2)	
Others	323	258 (79.9)	171	131 (76.6)	
Stage					
I - IIIA	655	315 (48.1)	606	352 (58.0)	0.003
IIIB - IV	528	482 (91.3)	377	313 (83.0)	
Missing	2		--		

Abbreviations: PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. HLCS, Harvard Lung Cancer Suceptibility.
*Chi-square test for the comparison of the characteristics between the PLCO trial and Harvard study for each clinical variable.

Supplementary Table 2. List of 98 selected genes in the GnRH signaling pathway gene-set used in the discovery analysis

Dataset	Name of pathway[a]	Selected genes	Number of genes
KEGG	GNRH_SIGNALING_PATHWAY	*ADCY1, ADCY2, ADCY3, ADCY4, ADCY5, ADCY6, ADCY7, ADCY8, ADCY9, ATF4, CACNA1C, CACNA1D, CACNA1F*[b]*, CACNA1S, CALM1, CALM2, CALM3, CALML3, CALML5, CALML6, CAMK2A, CAMK2B, CAMK2D, CAMK2G, CDC42, CGA, EGFR, ELK1*[b]*, FSHB, GNA11, GNAQ, GNAS, GNRH1, GNRH2, GNRHR, GRB2, HBEGF, HRAS, ITPR1, ITPR2, ITPR3, JMJD7-PLA2G4B, JUN, KRAS, LHB, MAP2K1, MAP2K2, MAP2K3, MAP2K4, MAP2K6, MAP2K7, MAP3K1, MAP3K2, MAP3K3, MAP3K4, MAPK1, MAPK10, MAPK11, MAPK12, MAPK13, MAPK14, MAPK3, MAPK7, MAPK8, MAPK9, MMP14, MMP2, NRAS, PLA2G10, PLA2G12A, PLA2G12B, PLA2G1B, PLA2G2A, PLA2G2C, PLA2G2D, PLA2G2E, PLA2G2F, PLA2G3, PLA2G4A, PLA2G4B, PLA2G4E, PLA2G5, PLA2G6, PLCB1, PLCB2, PLCB3, PLCB4, PLD1, PLD2, PRKACA, PRKACB, PRKACG, PRKCA, PRKCB, PRKCD, PRKX*[b]*, PTK2B, RAF1, SOS1, SOS2, SRC*	101
Total			101

[a] Genes were selected based on online datasets.

[b] Genes in X chromosome had been removed.

Keyword: GNRH

Organism: Homo sapiens

Supplementary Table 3. Associations of the first 10 principal components and OS of NSCLC in the PLCO trial

PC*	Parameter Estimate	Standard Error	Chi-Square	*P*
PC1	4.821	1.353	12.697	<0.001
PC2	-0.681	1.228	0.308	0.579
PC3	-3.054	0.949	10.351	0.001
PC4	-2.837	1.246	5.184	0.023
PC5	-0.910	1.232	0.546	0.460
PC6	1.355	1.252	1.172	0.279
PC7	-0.236	1.218	0.038	0.846
PC8	-1.684	1.322	1.622	0.203
PC9	-1.886	1.267	2.216	0.137
PC10	0.347	1.240	0.078	0.180

Abbreviations: OS, overall survival; NSCLC, non-small cell lung cancer; PLCO, the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; PC, principal component.

*The first 4 were used for the adjustment for population stratification in the multivariate analysis.

Supplementary Table 4. Function prediction of the seven validated SNPs associated with survival of NSCLC Data obtained from RegulomeDB[1] and Haploreg v4.1

SNP	Genes	LD (r^2)	Chr.	RegDB[1]	Epigenome ID (EID)	Description	H3K4me1[2]	H3K4me3	H3K27ac[2]	Motifs changed	selected eQTL hits
rs4150236	*HBEGF*	1	5	5	E096	Lung	H3K4me1_Enh		H3K27ac_Enh	5 altered motifs	14 hits
rs4150230	*HBEGF*	0.93	5	5	E096	Lung				5 altered motifs	19 hits
rs4150232	*HBEGF*	0.91	5	6	E096	Lung				BDP1, GR, LUN-1	19 hits
rs4150234	HBEGF	0.96	5	6	E096	Lung	H3K4me1_Enh			6 altered motifs	18 hits
rs13385	HBEGF	0.96	5	4	E096	Lung	H3K4me1_Enh			EBF, PRDM1	21 hits
rs2237078	HBEGF	0.91	5	6	E096	Lung				11 altered motifs	20 hits
rs116454384	*ITPR3*		6	5	E114	A549 EtOH 0.02pct Lung Carcinoma Cell Line	H3K4me1_Enh		H3K27ac_Enh	32 altered motifs	9 hits

1 RegulomeDB: http://regulomedb.org/

2 Haploreg:http://archive.broadinstitute.org/mammals/haploreg/haploreg.php

Abbreviations: NSCLC: non-small cell lung cancer; SNP, single nucleotide polymorphism; LD: linkage disequilibrium; Chr.: chromosome; H3K4me1: monomethylation of the 4th lysine of histone 3; H3K4me3: histone H3 lysine 4 trimethylation; H3K27ac: acetylation of histone H3 lysine 27; eQTL: expression quantitative trait loci.

Supplementary Table 5. Stratified analysis for association between the protective genotypes and survival of NSCLC patients in the PLCO trial[a]

Characteristics	OS							DSS						
	0 protective genotypes[b]		1-2 protective genotypes[b]		Multivariate analysis[c]		P_{inter}[d]	0 protective Genotypes[b]		1-2 protective genotypes[b]		Multivariate analysis[c]		P_{inter}[d]
	All	Death (%)	All	Death (%)	HR (95% CI)	*P*		All	Death (%)	All	Death (%)	HR (95% CI)	*P*	
Age (years)														
≤ 71	266	188 (70.7)	368	211 (57.3)	0.77 (0.63-0.94)	**0.012**		266	170 (63.9)	368	189 (51.4)	0.78 (0.63-0.97)	**0.023**	
> 71	223	166 (74.4)	318	224 (70.4)	0.78 (0.63-0.96)	**0.020**	0.896	223	154 (69.1)	318	196 (61.6)	0.74 (0.60-0.93)	**0.008**	0.497
Sex														
Male	289	221 (76.5)	406	284 (70.0)	0.73 (0.61-0.87)	**0.0006**		289	200 (69.2)	406	244 (60.1)	0.71 (0.58-0.86)	**0.0005**	
Female	200	133 (66.5)	280	151 (53.9)	0.83 (0.64-1.06)	0.130	0.465	200	124 (62.0)	280	141 (50.4)	0.82 (0.64-1.06)	0.134	0.334
Smoking status														
Never	49	34 (69.4)	65	28 (43.1)	0.57 (0.32-1.00)	0.049		49	32 (65.3)	65	28 (43.1)	0.60 (0.34-1.06)	0.076	
Former	277	206 (74.4)	367	255 (69.5)	0.78 (0.65-0.94)	**0.010**		277	187 (67.5)	367	227 (61.9)	0.78 (0.64-0.95)	**0.012**	
Current	163	114 (69.9)	254	152 (59.8)	0.76 (0.60-0.98)	**0.034**	0.160	163	105 (64.4)	254	130 (51.2)	0.74 (0.57-0.96)	**0.024**	0.147
Histology														
AD	230	147 (63.9)	345	199 (57.7)	0.76 (0.61-0.94)	**0.013**		230	135 (58.7)	345	186 (53.9)	0.78 (0.62-0.98)	**0.033**	
SC	107	77 (72.0)	177	114 (64.4)	0.63 (0.46-0.86)	**0.004**		107	70 (65.4)	177	91 (51.4)	0.54 (0.39-0.76)	**0.0004**	
Others	152	130 (85.5)	164	122 (74.4)	0.83 (0.64-1.07)	0.143	0.851	152	119 (78.3)	164	108 (65.9)	0.83 (0.63-1.08)	0.166	0.862
Tumor stage														
I-IIIA	260	139 (53.5)	394	175 (44.4)	0.78 (0.62-0.97)	**0.028**		260	119 (45.8)	394	134 (34.0)	0.71 (0.56-0.92)	**0.008**	
IIIB-IV	229	215 (93.9)	292	260 (89.0)	0.78 (0.65-0.94)	**0.011**	0.562	229	205 (89.5)	292	251 (86.0)	0.80 (0.66-0.97)	**0.023**	0.747
Chemotherapy														
No	256	161 (62.9)	382	205 (53.7)	0.77 (0.63-0.96)	**0.019**		256	140 (54.7)	382	167 (43.7)	0.75 (0.59-0.94)	**0.014**	
Yes	233	193 (82.8)	304	230 (75.7)	0.74 (0.61-0.90)	**0.003**	0.790	233	184 (79.0)	304	218 (71.7)	0.74 (0.61-0.91)	**0.004**	0.515
Radiotherapy														
No	306	202 (66.0)	455	247 (54.3)	0.76 (0.63-0.92)	**0.004**			181 (59.2)	455	210 (46.2)	0.76 (0.62-0.93)	**0.007**	
Yes	183	152 (83.1)	231	188 (81.4)	0.72 (0.58-0.91)	**0.005**	0.818	183	143 (78.1)	231	175 (75.8)	0.72 (0.57-0.91)	**0.005**	0.815
Surgery														
No	279	252 (90.3)	356	313 (87.9)	0.81 (0.68-0.96)	**0.014**		279	239 (85.7)	356	295 (82.9)	0.81 (0.68-0.96)	**0.016**	
Yes	210	102 (48.6)	330	122 (37.0)	0.71 (0.54-0.92)	**0.011**	0.374	210	85 (40.5)	330	90 (27.3)	0.65 (0.48-0.88)	**0.006**	0.173

Abbreviations: NSCLC, non-small cell lung cancer; PLCO, the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; OS, overall survival; DSS, disease-specific survival; HR, hazards ratio; CI, confidence interval; AD, adenocarcinoma; SC, squamous cell carcinoma;

[a]10 missing date were excluded;

[b]Protective genotypes were *HBEGF* rs4150236 GA/AA and *ITPR3* rs116454384 CT/TT;

[c]Adjusted for age, sex, stage, histology, smoking status, chemotherapy, radiotherapy, surgery, PC1, PC2, PC3, and PC4;

[d]*P*inter: *P* value for interaction analysis between characteristic and risk genotypes.

Supplementary Table 5. Stratified analysis for association between the *HBEGF* rs4150236 and survival of NSCLC in the PLCO trial[a]

Characteristics	OS							DSS						
	GG genotype		GA/AA genotypes		Multivariate analysis[b]		P_{inter}[c]	GG Genotype		GA/AA genotypes		Multivariate analysis[b]		P_{inter}[c]
	All	Death (%)	All	Death (%)	HR (95% CI)	*P*		All	Death (%)	All	Death (%)	HR (95% CI)	*P*	
Age (years)														
≤ 71	391	260 (66.5)	243	139 (57.2)	0.82 (0.67-1.02)	0.070		391	236 (60.4)	243	123 (50.6)	0.82 (0.65-1.02)	0.074	
> 71	322	240 (74.5)	219	150 (68.5)	0.81 (0.66-1.00)	0.050	0.810	322	217 (67.4)	219	133 (60.7)	0.79 (0.63-0.99)	**0.037**	0.461
Sex														
Male	431	327 (75.9)	264	178 (67.4)	0.74 (0.62-0.90)	**0.002**		431	327 (75.9)	264	178 (67.4)	0.72 (0.59-0.88)	**0.001**	
Female	282	173 (61.4)	198	111 (56.1)	0.95 (0.74-1.22)	0.682	0.196	282	173 (61.4)	198	111 (56.1)	0.96 (0.74-1.25)	0.784	0.112
Smoking status														
Never	62	40 (64.5)	52	22 (42.3)	0.55 (0.30-1.00)	0.050		62	38 (61.3)	52	22 (42.3)	0.58 (0.31-1.06)	0.077	
Former	409	300 (73.4)	235	161 (68.5)	0.77 (0.63-0.94)	**0.009**		409	270 (66.0)	235	144 (61.3)	0.78 (0.63-0.96)	**0.019**	
Current	242	160 (66.1)	175	106 (60.6)	0.91 (0.71-1.17)	0.461	0.285	242	145 (59.9)	175	90 (51.4)	0.86 (0.66-1.12)	0.267	0.220
Histology														
AD	329	205 (62.3)	246	141 (57.3)	0.85 (0.68-1.05)	0.135		329	190 (57.8)	246	131 (53.3)	0.84 (0.67-1.06)	0.135	
SC	174	121 (69.5)	110	70 (63.6)	0.64 (0.47-0.88)	**0.006**		174	106 (60.9)	110	55 (50.0)	0.57 (0.41-0.81)	**0.002**	
Others	210	174 (82.9)	106	78 (73.6)	0.92 (0.70-1.22)	0.564	0.951	210	157 (74.8)	106	70 (66.0)	0.92 (0.69-1.24)	0.588	0.959
Tumor stage														
I-IIIA	390	203 (52.1)	264	111 (42.1)	0.71 (0.56-0.90)	**0.004**		390	203 (52.1)	264	111 (42.1)	0.64 (0.49-0.84)	**0.001**	
IIIB-IV	323	297 (92.0)	198	178 (89.9)	0.88 (0.72-1.06)	**0.177**	0.328	323	297 (92.0)	198	178 (89.9)	0.89 (0.73-1.08)	0.236	0.102
Chemotherapy														
No	379	231 (61.0)	259	135 (52.1)	0.80 (0.65-1.00)	0.046		379	231 (61.0)	259	135 (52.1)	0.78 (0.62-0.99)	0.040	
Yes	334	269 (80.5)	203	154 (75.9)	0.78 (0.64-0.96)	**0.019**	0.665	334	269 (80.5)	203	154 (75.9)	0.84 (0.68-0.97)	**0.026**	0.460
Radiotherapy														
No	455	283 (62.2)	306	166 (54.3)	0.85 (0.70-1.03)	0.102		455	283 (62.2)	306	166 (54.3)	0.84 (0.68-1.03)	0.100	
Yes	258	217 (84.1)	156	123 (78.9)	0.73 (0.58-0.92)	**0.008**	0.412	258	217 (84.1)	156	123 (78.9)	0.74 (0.58-0.94)	**0.012**	0.520
Surgery														
No	393	357 (90.8)	242	208 (86.0)	0.85 (0.71-1.01)	0.069		393	357 (90.8)	242	208 (86.0)	0.85 (0.71-1.02)	0.087	
Yes	320	143 (44.7)	220	81 (36.8)	0.76 (0.58-1.00)	0.052	0.344	320	143 (44.7)	220	81 (36.8)	0.69 (0.50-0.94)	**0.020**	0.139

Abbreviations: NSCLC, non-small cell lung cancer; PLCO, the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; OS, overall survival; DSS, disease-specific survival; HR, hazards ratio; CI, confidence interval; AD, adenocarcinoma; SC, squamous cell carcinoma.

[a] 10 missing date were excluded;

[b] Adjusted for age, sex, stage, histology, smoking status, chemotherapy, radiotherapy, surgery, PC1, PC2, PC3, and PC4;

[c] *P*inter: *P* value for interaction analysis between characteristic and protective genotypes.

Supplementary Table 6. Stratified analysis for association between the *ITPR3* rs116454384 and survival of NSCLC in the PLCO trial

Characteristics[a]	OS							DSS						
	CC genotype		CT/TT genotypes		Multivariate analysis[b]		P_{inter}[c]	CC Genotype		CT/TT genotypes		Multivariate analysis[b]		P_{inter}[c]
	All	Death (%)	All	Death (%)	HR (95% CI)	*P*		All	Death (%)	All	Death (%)	HR (95% CI)	*P*	
Age (years)														
≤ 71	430	280 (65.1)	204	119 (58.3)	0.85 (0.69-1.06)	0.148		430	250 (58.1)	204	109 (53.4)	0.88 (0.70-1.11)	0.274	
> 71	374	270 (72.2)	167	120 (71.9)	0.88 (0.70-1.10)	0.248	0.956	374	249 (66.6)	167	101 (60.5)	0.81 (0.63-1.03)	0.083	0.659
Sex														
Male	459	334 (72.8)	236	171 (72.5)	0.87 (0.73-1.06)	0.161		459	334 (72.8)	236	171 (72.5)	0.84 (0.69-1.03)	0.095	
Female	345	216 (62.6)	135	68 (50.4)	0.80 (0.61-1.07)	0.132	0.780	345	216 (62.6)	135	68 (50.4)	0.80 (0.60-1.07)	0.132	0.997
Smoking status														
Never	90	51 (56.7)	24	11 (45.8)	0.85 (0.40-1.80)	0.676		90	49 (54.4)	24	11 (45.8)	0.93 (0.44-1.97)	0.842	
Former	429	307 (71.6)	215	154 (71.6)	0.98 (0.80-1.19)	0.821		429	281 (65.5)	215	133 (61.9)	0.92 (0.74-1.13)	0.391	
Current	285	192 (67.4)	132	74 (56.1)	0.66 (0.50-0.88)	**0.004**	0.201	285	169 (59.3)	132	66 (50.0)	0.69 (0.52-0.93)	**0.013**	0.472
Histology														
AD	411	251 (61.1)	164	95 (57.9)	0.76 (0.59-0.97)	**0.027**		411	230 (56.0)	164	91 (55.5)	0.80 (0.62-1.03)	0.085	
SC	175	119 (68.0)	109	72 (66.1)	0.85 (0.63-1.15)	0.292		175	105 (60.0)	109	56 (51.4)	0.72 (0.51-1.01)	0.053	
Others	218	180 (82.6)	98	72 (73.5)	0.91 (0.69-1.20)	0.502	0.583	218	164 (75.2)	98	63 (64.3)	0.90 (0.67-1.21)	0.478	0.942
Tumor stage														
I-IIIA	442	214 (48.4)	212	100 (47.2)	0.98 (0.77-1.25)	0.895		442	214 (48.4)	212	100 (47.2)	0.95 (0.72-1.25)	0.703	
IIIB-IV	362	336 (92.8)	159	139 (87.4)	0.82 (0.67-1.01)	0.058	0.153	362	336 (92.8)	159	139 (87.4)	0.82 (0.67-1.01)	0.067	0.333
Chemotherapy														
No	440	258 (58.6)	198	108 (54.6)	0.87 (0.69-1.09)	0.231		440	258 (58.6)	198	108 (54.6)	0.83 (0.64-1.07)	0.143	
Yes	364	292 (80.2)	173	131 (75.7)	0.85 (0.69-1.05)	0.129	0.977	364	292 (80.2)	173	131 (75.7)	0.85 (0.68-1.05)	0.127	0.744
Radiotherapy														
No	521	314 (60.3)	240	135 (56.3)	0.89 (0.72-1.09)	0.255		521	314 (60.3)	240	135 (56.3)	0.86 (0.69-1.08)	0.193	
Yes	283	236 (83.4)	131	104 (79.4)	0.80 (0.63-1.01)	0.064	0.482	283	236 (83.4)	131	104 (79.4)	0.79 (0.62-1.02)	0.066	0.624
Surgery														
No	436	392 (89.9)	199	173 (86.9)	0.84 (0.70-1.01)	0.065		436	392 (89.9)	199	173 (86.9)	0.84 (0.70-1.02)	0.075	
Yes	368	158 (42.9)	172	66 (38.4)	0.88 (0.66-1.18)	0.397	0.682	368	158 (42.9)	172	66 (38.4)	0.81 (0.58-1.14)	0.229	0.928

Abbreviations: NSCLC, non-small cell lung cancer; PLCO, the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; OS, overall survival; DSS, disease-specific survival; HR squamous cell carcinoma.

[a] 10 missing date were excluded;

[b] Adjusted for age, sex, stage, histology, smoking status, chemotherapy, radiotherapy, surgery, PC1, PC2, PC3, and PC4;

[c] *P*inter: *P* value for interaction analysis between characteristic and protective genotypes.

Supplemental Acknowledgements

We wish to thank all of the investigators and funding agencies that enabled the deposition of data in dbGaP and PLCO that we used in the present study:

The datasets used for the analyses described in thr present study were obtained from dbGaP at http://www.ncbi.nlm.nih.gov/gap through dbGaP accession number phs000336.v1.p1 and phs000093.v2.p2. Principal Investigators: Maria Teresa Landi. Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA. Neil E. Caporaso. Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA.

Funding support for the GWAS of Lung Cancer and Smoking was provided through the NIH Genes, Environment and Health Initiative [GEI] (Z01 CP 010200). The human subjects participating in the GWAS derive from The Environment and Genetics in Lung Cancer Etiology (EAGLE) case-control study and the Prostate, Lung Colon and Ovary Screening Trial and these studies are supported by intramural resources of the National Cancer Institute. Assistance with phenotype harmonization and genotype cleaning, as well as with general study coordination, was provided by the Gene Environment Association Studies, GENEVA Coordinating Center (U01HG004446). Assistance with data cleaning was provided by the National Center for Biotechnology Information. Funding support for genotyping, which was performed at the Johns Hopkins University Center for Inherited Disease Research, was provided by the NIH GEI (U01HG004438).

PLCO was also supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics and by contracts from the Division of Cancer Prevention, National Cancer Institute, NIH, DHHS. The authors thank PLCO screening center investigators and staff, and the staff of Information Management Services Inc. and Westat Inc. Most importantly, we acknowledge trial participants for their contributions that made this study possible.