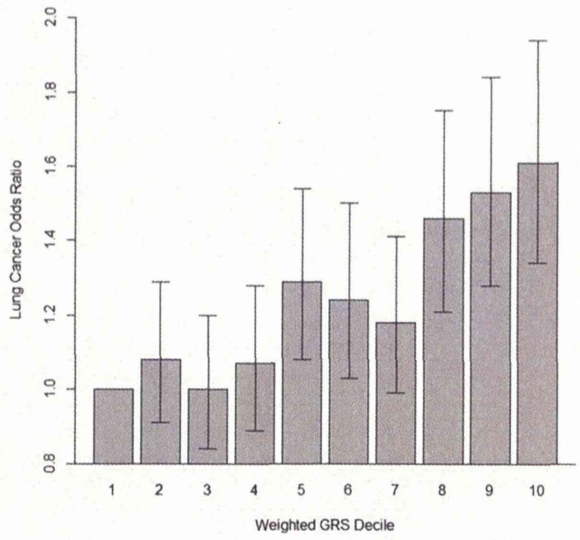

Figure 3. Adjusted odds ratios of weighted telomere length genetic risk scores with lung cancer risk among never-smoking females in Asia, by decile. Bars are lung cancer association odds ratios for each weighted GRS decile and error bars represent 95% confidence intervals around the odds ratios. The first decile is used as the reference group with an odds ratio of one. As compared to individuals with a telomere-length associated GRS in the first decile, individuals with a GRS in the tenth decile have a 61% (95% CI = 34–94%, p value = 2.83×10^{-7}) increased odds of developing lung cancer.

Additional age-stratified analyses were conducted to investigate potential differences in the weighted GRS lung cancer association with age. Results indicate women in the younger than 60 years age group had an odds ratio of 1.72 (95% CI = 1.46–2.02, p value = 9.35×10^{-11}) comparing women in the fourth and first quartiles of weighted GRS, whereas women in the 60 years or older age group had an odds ratio of 1.33 (95% CI = 1.12–1.57, p value = 0.001). A significant difference was observed between the two effect estimates (p value = 0.03) indicating the association between weighted telomere-associated GRS and lung cancer risk may be stronger in younger women. Analyses were also stratified based on the two primary histological subtypes of lung cancer: adenocarcinoma and squamous cell carcinoma. The weighted GRS odds ratio comparing the fourth to first quartile for adenocarcinoma cases was 1.51 (95% CI = 1.33–1.72, p value = 2.82×10^{-10}). The squamous cell carcinoma odds ratio estimate was slightly lower at 1.42 (95% CI = 1.10–1.81, p value = 0.006). A case-only analysis of the two histological subtypes found no significant difference in weighted GRS effect (p value = 0.80).

Discussion

Our study investigated the relationship between seven telomere-length associated variants and lung cancer risk. Aggregations of the seven variants were highly associated with lung cancer risk with the direction of the associations indicating that longer telomere length, as predicted by higher telomere length associated GRS, is a risk factor for lung cancer. Although the telomere-length associated variants explained only a fraction of the variation in telomere length, the associations suggest genetic effects tagged by these variants are important for lung cancer risk.

Previous studies have demonstrated an association with the *TERT* locus (rs2736100)[21,27] and lung cancer risk, however, our study is the first to provide evidence for associations with other telomere-length associated variants. In particular, the nominal significance of the *TERC* locus (rs10936599) suggests this locus may play a role in telomere-related maintenance important for lung cancer risk, although further studies are needed to verify this association. The seven telomere-length associated variants explain a limited amount of the total variation in telomere length, suggesting that additional variation in telomere length may be attributable to other genetic variants which remain to be discovered. Additionally, the lower association p values of aggregate association tests relative to the telomere-length specific GRS tests suggests that in addition to telomere length other aspects of telomeres, such as maintenance of genome stability or chromosomal repair, or distinct biological process tagged by these telomere-length associated variants, especially rs2736100 in *TERT*, may be important contributors to the lung cancer risk.

Using telomere-length associated genetic variants as an instrument for measuring telomere length provides several advantages. First, reverse causation biases that may influence case-control studies of telomere length and disease can be eliminated since telomere-length associated variants are unrelated to time of blood draw and disease diagnosis. Also, by using a correlated genetic proxy for telomere length, it may be possible to partition genetic versus other risk factors (*e.g.*, aging, oxidative damage) that are reflected in the telomere length phenotype. One potential confounder in our analysis is correlated population specific differences between lung cancer frequency and telomere risk allele frequencies. However, this potential population stratification bias was mitigated by adjusting for all principal components that were significantly associated with lung cancer risk.

The biological mechanism linking longer telomere length to lung carcinogenesis is unclear. Although telomere attrition leads to replicative senescence and apoptosis, telomere elongation may result in immortalized cells with unregulated telomerase activity and unlimited potential for cellular and tumor growth.[28–31] Shorter telomeres may act as tumor suppressors, whereas longer telomeres may not. In addition, recent evidence suggests excessively long telomeres may be as important for chromosomal instability as critically short telomeres.[32]

Our results, as well as an example from coronary artery disease,[20] suggest the seven telomere-associated variants are

useful proxies for investigating telomere length in a variety of diseases. Although the seven variants explain a small portion of measured peripheral WBC telomere length, the age-related shortening per variant risk allele (1.9–3.9 years) and equivalent changes in telomere base pair length (57–117 bases) appear to be biologically meaningful for disease risk.[20] Evidence from our analysis suggests that these seven telomere-associated variants, discovered in a European population, also have application to Asian populations. Additionally, the effect of the weighted GRS appears stronger in younger individuals suggesting telomere-length associated GRSs may be more useful in younger populations with fewer accumulated environmental exposures affecting telomere length than in older populations.

Results from our study indicate the variation tagged by seven telomere-length associated variants is important for lung cancer risk. Our genetic-based proxy for telomere length suggests longer telomere length is associated with increased lung cancer risk in non-smoking Asian females which is consistent with evidence from a number of relatively small prospective studies of measured telomere length and lung cancer risk with non-smoking cases in Asia and mostly ever-smoking cases of European descent.[17] Further studies investigating the biological mechanisms related to the variation in telomere length captured by these genetic variants will improve understanding of the molecular pathways linking telomere length to lung cancer risk and may elucidate important preventative and therapeutic targets.

References

1. Blasco MA. Telomeres and human disease: ageing, cancer and beyond. *Nat Rev Genet* 2005;6: 611–22.
2. Jang JS, Choi YY, Lee WK, et al. Telomere length and the risk of lung cancer. *Cancer Sci* 2008;99: 1385–9.
3. Willeit P, Willeit J, Mayr A, et al. Telomere length and risk of incident cancer and cancer mortality. *JAMA* 2010;304:69–75.
4. Ma H, Zhou Z, Wei S, et al. Shortened telomere length is associated with increased risk of cancer: a meta-analysis. *PloS One* 2011;6:e20466.
5. Wentzensen IM, Mirabello L, Pfeiffer RM, et al. The association of telomere length and cancer: a meta-analysis. *Cancer Epidemiol Biomarkers Prevent Publ Am Assoc Cancer Res* 2011;20:1238–50.
6. McGrath M, Wong JY, Michaud D, et al. Telomere length, cigarette smoking, and bladder cancer risk in men and women. *Cancer Epidemiol Biomarkers Prevent Publ Am Assoc Cancer Res* 2007;16:815–9.
7. Pellatt AJ, Wolff RK, Torres-Mejia G, et al. Telomere length, telomere-related genes, and breast cancer risk: the breast cancer health disparities study. *Genes Chromosomes Cancer* 2013;52:595–609.
8. Qu S, Wen W, Shu XO, et al. Association of leukocyte telomere length with breast cancer risk: nested case-control findings from the Shanghai women's health study. *Am J Epidemiol* 2013;177: 617–24.
9. Lan Q, Cawthon R, Shen M, et al. A prospective study of telomere length measured by monochrome multiplex quantitative PCR and risk of non-hodgkin lymphoma. *Clin Cancer Res Off J Am Assoc Cancer Res* 2009;15:7429–33.
10. Lynch SM, Major JM, Cawthon R, et al. A prospective analysis of telomere length and pancreatic cancer in the alpha-tocopherol beta-carotene cancer (ATBC) prevention study. *Int J Cancer J Int Du Cancer* 2013;133:2672–80.
11. Gramatges MM, Telli ML, Balise R, et al. Longer relative telomere length in blood from women with sporadic and familial breast cancer compared with healthy controls. *Cancer Epidemiol Biomarkers Prevent Publ Am Assoc Cancer Res* 2010;19:605–13.
12. Nan H, Du M, De Vivo I, et al. Shorter telomeres associate with a reduced risk of melanoma development. *Cancer Res* 2011; 71:6758–63.
13. Svenson U, Ljungberg B, Roos G. Telomere length in peripheral blood predicts survival in clear cell renal cell carcinoma. *Cancer Res* 2009; 69:2896–901.
14. Walsh KM, Codd V, Smirnov IV, et al. Variants near TERT and TERC influencing telomere length are associated with high-grade glioma risk. *Nat Genet* 2014;46:731–5.
15. Lan Q, Cawthon R, Gao Y, et al. Longer telomere length in peripheral white blood cells is associated with risk of lung cancer and the rs2736100 (CLPTM1L-TERT) polymorphism in a prospective cohort study among women in china. *PloS One* 2013;8:e59230.
16. Shen M, Cawthon R, Rothman N, et al. A prospective study of telomere length measured by monochrome multiplex quantitative PCR and risk of lung cancer. *Lung Cancer* 2011;73:133–7.
17. Seow WJ, Cawthon RM, Purdue MP, et al. Telomere length in white blood cell DNA and lung cancer: a pooled analysis of three prospective cohorts. *Cancer Res* 2014;74:4090–8.
18. Sanchez-Espiridion B, Chen M, Chang JY, et al. Telomere length in peripheral blood leukocytes and lung cancer risk: a large case-control study in Caucasians. *Cancer Res* 2014;74:2476–86.
19. Cawthon RM. Telomere length measurement by a novel monochrome multiplex quantitative PCR method. *Nucleic Acids Res* 2009;37:e21
20. Codd V, Nelson CP, Albrecht E, et al. Identification of seven loci affecting mean telomere length and their association with disease. *Nat Genet* 2013;45:422–7. 7e1-2.
21. Lan Q, Hsiung CA, Matsuo K, et al. Genome-wide association analysis identifies new lung cancer susceptibility loci in never-smoking women in Asia. *Nat Genet* 2012;44:1330–5.
22. 1000 Genomes Project Consortium, Abecasis GR, Altshuler D, et al. A map of human genome variation from population-scale sequencing. *Nature* 2010;467:1061–73.
23. Wang Z, Jacobs KB, Yeager M, et al. Improved imputation of common and uncommon SNPs with a new reference set. *Nat Genet* 2012;44:6–7.
24. R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2013.
25. Wu MC, Kraft P, Epstein MP, et al. Powerful SNP-set analysis for case-control genome-wide association studies. *Am J Hum Genet* 2010;86: 929–42.
26. Wu MC, Lee S, Cai T, et al. Rare-variant association testing for sequencing data with the sequence kernel association test. *Am J Hum Genet* 2011;89:82–93.
27. McKay JD, Hung RJ, Gaborieau V, et al. Lung cancer susceptibility locus at 5p15.33. *Nat Genet* 2008;40:1404–6.
28. Hackett JA, Greider CW. Balancing instability: dual roles for telomerase and telomere dysfunction in tumorigenesis. *Oncogene* 2002;21:619–26.
29. Reddel RR. The role of senescence and immortalization in carcinogenesis. *Carcinogenesis* 2000;21: 477–84.
30. Kim NW, Piatyszek MA, Prowse KR, et al. Specific association of human telomerase activity with immortal cells and cancer. *Science* 1994;266: 2011–5.
31. Mooi WJ, Peeper DS. Oncogene-induced cell senescence–halting on the road to cancer. *N Engl J Med* 2006;355:1037–46.
32. Bull CF, Mayrhofer G, O'Callaghan NJ, et al. Folate deficiency induces dysfunctional long and short telomeres: both states are associated with hypomethylation and DNA damage in human WIL2-NS cells. *Cancer Prevent Res* 2014;7:128–38.

Hum Genet (2015) 134:333–341
DOI 10.1007/s00439-014-1528-z

ORIGINAL INVESTIGATION

Interactions between household air pollution and GWAS-identified lung cancer susceptibility markers in the Female Lung Cancer Consortium in Asia (FLCCA)

H. Dean Hosgood III · Minsun Song · Chao Agnes Hsiung · Zhihua Yin · Xiao-Ou Shu · Zhaoming Wang · Nilanjan Chatterjee · Wei Zheng · Neil Caporaso · Laurie Burdette · Meredith Yeager · Sonja I. Berndt · Maria Teresa Landi · Chien-Jen Chen · Gee-Chen Chang · Chin-Fu Hsiao · Ying-Huang Tsai · Li-Hsin Chien · Kuan-Yu Chen · Ming-Shyan Huang · Wu-Chou Su · Yuh-Min Chen · Chung-Hsing Chen · Tsung-Ying Yang · Chih-Liang Wang · Jen-Yu Hung · Chien-Chung Lin · Reury-Perng Perng · Chih-Yi Chen · Kun-Chieh Chen · Yao-Jen Li · Chong-Jen Yu · Yi-Song Chen · Ying-Hsiang Chen · Fang-Yu Tsai · Christopher Kim · Wei Jie Seow · Bryan A. Bassig · Wei Wu · Peng Guan · Qincheng He · Yu-Tang Gao · Qiuyin Cai · Wong-Ho Chow · Yong-Bing Xiang · Dongxin Lin · Chen Wu · Yi-Long Wu · Min-Ho Shin · Yun-Chul Hong · Keitaro Matsuo · Kexin Chen · Maria Pik Wong · Dara Lu · Li Jin · Jiu-Cun Wang · Adeline Seow · Tangchun Wu · Hongbing Shen · Joseph F. Fraumeni Jr · Pan-Chyr Yang · I-Shou Chang · Baosen Zhou · Stephen J. Chanock · Nathaniel Rothman · Qing Lan

Received: 23 October 2014 / Accepted: 29 December 2014 / Published online: 8 January 2015

Abstract We previously carried out a multi-stage genome-wide association study (GWAS) on lung cancer among never smokers in the Female Lung Cancer Consortium in Asia (FLCCA) (6,609 cases, 7,457 controls) that identified novel susceptibility loci at 10q25.2, 6q22.2, and 6p21.32, and confirmed two previously identified loci at 5p15.33 and 3q28. Household air pollution (HAP) attributed to solid fuel burning for heating and cooking, is the leading cause of the overall disease burden in Southeast Asia, and is known to contain lung carcinogens. To evaluate the gene–HAP interactions associated with lung cancer in loci independent of smoking, we analyzed data from studies participating in FLCCA with fuel use information available (n = 3; 1,731 cases; 1,349 controls). Coal use was associated with a 30 % increased risk of lung cancer (OR 1.3, 95 % CI 1.0–1.6). Among the five a priori SNPs

H. D. Hosgood, M. Song, Z. Yin, X.-O. Shu and Z. Wang contributed equally. I.-S. Chang, C. A. Hsiung, P.-C. Yang, B. Zhou, S. J. Chanock, N. Rothman and Q. Lan contributed equally.

Electronic supplementary material The online version of this article (doi:10.1007/s00439-014-1528-z) contains supplementary material, which is available to authorized users.

H. D. Hosgood III (✉)
Department of Epidemiology and Population Health, Albert Einstein College of Medicine, 1300 Morris Park Ave. Belfer 1309, 10461 Bronx, NY, USA
e-mail: dean.hosgood@einstein.yu.edu

H. D. Hosgood III · M. Song · N. Chatterjee · N. Caporaso · S. I. Berndt · M. T. Landi · C. Kim · W. J. Seow · B. A. Bassig · J. F. Fraumeni Jr · S. J. Chanock · N. Rothman · Q. Lan
Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD, USA

C. A. Hsiung · C.-F. Hsiao · L.-H. Chien · Y.-S. Chen · Y.-H. Chen
Institute of Population Health Sciences, National Health Research Institutes, Zhunan, Taiwan

Z. Yin · W. Wu · P. Guan · Q. He · B. Zhou
Department of Epidemiology, School of Public Health, China Medical University, Shenyang, China

X.-O. Shu · W. Zheng · Q. Cai
Division of Epidemiology, Department of Medicine, Vanderbilt University Medical Center and Vanderbilt-Ingram Cancer Center, Nashville, TN, USA

Z. Wang · L. Burdette · M. Yeager
Core Genotype Facility, SAIC-Frederick, National Cancer Institute-Frederick, National Institutes of Health, Maryland, USA

C.-J. Chen · Y.-J. Li
Genomic Research Center, Academia Sinica, Taipei, Taiwan

G.-C. Chang
Department of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan

G.-C. Chang · T.-Y. Yang · K.-C. Chen
Division of Chest Medicine, Taichung Veterans General Hospital, Taichung, Taiwan

identified by our GWAS, two showed a significant interaction with coal use (*HLA Class II* rs2395185, $p = 0.02$; *TP63* rs4488809 (rs4600802), $p = 0.04$). The risk of lung cancer associated with coal exposure varied with the respective alleles for these two SNPs. Our observations provide evidence that genetic variation in *HLA Class II* and *TP63* may modify the association between HAP and lung cancer risk. The roles played in the cell cycle and inflammation pathways by the proteins encoded by these two genes provide biological plausibility for these interactions; however, additional replication studies are needed in other non-smoking populations.

Introduction

Genome-wide association studies (GWAS) of lung cancer, consisting primarily of smokers of Caucasian descent, identified susceptibility variants on 5p15 and 15q25 (Landi et al. 2009; Amos et al. 2008; Hung et al. 2008; Wang et al. 2008; Wu et al. 2009; Truong et al. 2010), providing insights into the underlying mechanism(s) of lung cancer susceptibility. It was unclear, however, if these genetic variations were associated with lung cancer and/or tobacco smoking (Chanock and Hunter 2008). Interestingly, we did not observe an association at the nicotine receptor coding region on 15q25 (Hsiung et al. 2010; Lan et al. 2012) in our Female Lung Cancer Consortium in Asia (FLCCA), which consists of epidemiological studies of lung cancer restricted to never-smoking female lung cancer cases and never-smoking female controls, suggesting that 15q25 is not associated with lung cancer independent of smoking. Further, our multi-stage GWAS of lung cancer among never smokers identified novel lung cancer susceptibility loci (Lan et al. 2012), which were not associated with lung cancer risk (i.e., $p \leq 10^{-8}$) in the GWAS consisting primarily of Caucasian smokers (Landi et al. 2009; Amos et al. 2008; Hung et al. 2008; Wang et al. 2008; Wu et al. 2009; Truong et al. 2010).

Lung cancer GWAS findings highlight the importance of accounting for environmental exposures, via study design or exposure assessment data, that may modify the genetic associations. We set out to evaluate the gene–environment interactions associated with lung cancer loci independent of smoking. Indoor emissions from household combustion of coal have been classified as carcinogenic to humans (IARC 2010). We pooled data on household air pollution (HAP) attributed to solid fuel burning for heating and cooking, which is the leading cause of disease in Southeast Asia (Lim et al. 2013), from three studies included in our GWAS.

Methods

Female Lung Cancer Consortium in Asia (FLCCA)

The Female Lung Cancer Consortium in Asia (FLCCA) consisting of epidemiological studies of lung cancer, which are restricted to never-smoking female lung cancer cases

Y.-H. Tsai
Department of Respiratory Therapy, Chang Gung Memorial Hospital, Chiayi, Taiwan

K.-Y. Chen · C.-J. Yu
Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

M.-S. Huang · J.-Y. Hung
Department of Internal Medicine, Kaohsiung Medical University Hospital, School of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

W.-C. Su · C.-C. Lin
Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, Cheng Kung University, Tainan, Taiwan

Y.-M. Chen · R.-P. Perng
Chest Department, Taipei Veterans General Hospital, Taipei, Taiwan

C.-H. Chen · F.-Y. Tsai · I.-S. Chang
National Institute of Cancer Research, National Health Research Institutes, Zhunan, Taiwan

C.-L. Wang
Department of Pulmonary and Critical Care, Chang Gung Memorial Hospital, Taoyuan, Taiwan

C.-Y. Chen
Cancer Center, China Medical University and Hospital, Taichung, Taiwan

Y.-T. Gao · Y.-B. Xiang
Department of Epidemiology, Shanghai Cancer Institute, Shanghai, China

W.-H. Chow
Department of Epidemiology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

D. Lin · C. Wu
State Key Laboratory of Molecular Oncology and Department of Etiology and Carcinogenesis, Cancer Institute and Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

and never-smoking female controls, was used for this research. To date, FLCCA includes 14 studies from Mainland China, Hong Kong, Taiwan, Singapore, Japan, and South Korea. FLCCA is comprised of over 6,600 cases, 7,400 controls (Lan et al. 2012).

Three studies in FLCCA contributed solid fuel use data to this pooling effort (Table 1). The studies, which have all been previously described, include the Genetic Epidemiological Study of Lung Adenocarcinoma (GELAC) from Taiwan (Jou et al. 2009), the Shenyang Lung Cancer Study (SLCS) (Yin et al. 2009), and the Shanghai Women's Health Cohort Study (SWHS) (Zhang et al. 2007; Zheng et al. 2005). In brief, the GELAC study recruited cases who were 18 years or more of age with incident primary lung cancer from six hospitals in Taiwan. Controls were cancer-free, randomly selected from the health examination clinics of the same hospitals during the same time period of case recruitment and frequency matched by age. The SLCS recruited cases with histologically confirmed lung cancers in Northeast China. Controls were selected from patients who were free of cancer history and symptom, and frequency matched to cases on age. The SWHS is a population-based cohort study of 75,221 women from Shanghai, China, aged 40–70 years. Participants for the current study were selected applying a nested case–control study design. Women with a newly diagnosed malignant neoplasm of the bronchus or lung after study recruitment were included in this study. Controls were selected among the study participants in the cohort who were cancer-free at the time of cancer diagnosis of the matched cases. For the SWHS, one control was randomly selected and matched with each case by age at baseline. After accounting for subjects with missing genotyping data and HAP data in all participating studies, we were left with an analytic data set of 1,731 cases and 1,349 controls.

Environmental exposure data

We utilized questionnaire data from each study to determine the type of fuel used for heating and/or cooking for each subject. The GELAC and SLCS studies provided information on the type of fuel used during cooking in their childhood home. SWHS provided information for fuel use for each subjects' most recent three residences lived. Fuel use data from each SWHS subject's oldest home was used to define the respective subject's fuel use. For all studies, subjects using any form of solid fuel, including coal, wood, and other forms of biomass, were classified as ever solid fuel users. Those not using these forms of fuel in their homes were classified as never solid fuel users. Ever solid fuel users were then refined into ever coal users if the specific type of fuel used in their home was coal. The questionnaires and interview methods have been previously reported for each of these studies (Jou et al. 2009; Yin et al. 2009; Zhang et al. 2007; Zheng et al. 2005). The main effects of solid fuel use and coal use were assessed by logistic regression, adjusting for age (categorical: less than 40, 40–49, 50–59, 60–69, more than 70) and study (GELAC, SLCS, SWHS).

Y.-L. Wu
Guangdong Lung Cancer Institute, Medical Research Center and Cancer Center of Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China

M.-H. Shin
Department of Preventive Medicine, Chonnam National University Medical School, Gwangju, Republic of Korea

Y.-C. Hong
Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea

K. Matsuo
Department of Preventive Medicine, Faculty of Medical Sciences, Kyushu University, Fukuoka, Japan

K. Chen
Department of Epidemiology and Biostatistics, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

M. P. Wong
Department of Pathology, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, China

D. Lu · L. Jin · J.-C. Wang
Ministry of Education Key Laboratory of Contemporary Anthropology and State Key Laboratory of Genetic Engineering, School of Life Sciences, Fudan University, Shanghai, China

A. Seow
Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore

T. Wu
Institute of Occupational Medicine and Ministry of Education Key Laboratory for Environment and Health, School of Public Health, Huazhong University of Science and Technology, Wuhan, China

H. Shen
Ministry of Education Key Laboratory of Modern Toxicology, Jiangsu Key Laboratory of Cancer Biomarkers, Prevention and Treatment, Nanjing Medical University, Nanjing, China

P.-C. Yang
Department of Internal Medicine, National Taiwan University College of Medicine, Taipei, Taiwan

Table 1 Studies from the Female Lung Cancer Consortium in Asia (FLCCA) that participated in a gene–environment interaction analysis of GWAS-identified SNPs that confer risk of never-smoking lung cancer and household air pollution

	Genetic epidemiological study of lung adenocarcinoma (GELAC)				Shenyang lung cancer study (SLCS)				Shanghai women's health cohort study (SWHS)				All studies			
	Cases		Controls		Cases		Controls		Cases		Controls		Cases		Controls	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Total subjects	1,098	100	1,019	100	549	100	260	100	84	100	70	100	1,731	100	1,349	100
Age[a]																
<59	504	45.9	479	47.0	282	51.4	127	48.8	40	47.6	31	44.3	826	47.7	637	47.2
≥59	594	54.1	540	53.0	267	48.6	133	51.2	44	52.4	39	55.7	905	52.3	712	52.8
Solid fuel use																
Ever	314	28.6	251	24.6	311	56.6	130	50.0	43	51.2	42	60.0	668	38.6	423	31.4
Never	784	71.4	768	75.4	238	43.4	130	50.0	41	48.8	28	40.0	1,063	61.4	926	68.6
Coal use																
Ever	69	6.3	46	4.5	58	10.6	100	38.5	43	51.2	42	60.0	365	21.1	188	13.9
Never	784	71.4	768	75.4	253	46.1	130	50.0	41	48.8	28	40.0	1,063	61.4	926	68.6
Environmental tobacco smoke																
Ever	767	69.9	615	60.4	481	87.6	222	85.4	59	70.2	53	75.7	1,307	75.5	890	66.0
Never	293	26.7	382	37.5	59	10.7	35	13.5	16	19.0	11	15.7	368	21.3	428	31.7
rs7086803																
GG	461	42.0	488	47.9	269	49.0	143	55.0	33	39.3	44	62.9	763	44.1	675	50.0
GA	459	41.8	415	40.7	239	43.5	105	40.4	38	45.2	21	30.0	736	42.5	541	40.1
AA	128	11.7	66	6.5	41	7.5	12	4.6	13	15.5	5	7.1	182	10.5	83	6.2
rs9387478																
AA	240	21.9	274	26.9	111	20.2	58	22.3	12	14.3	19	27.1	363	21.0	351	26.0
AC	548	49.9	518	50.8	281	51.2	135	51.9	39	46.4	38	54.3	868	50.1	691	51.2
CC	310	28.2	227	22.3	157	28.6	67	25.8	33	39.3	13	18.6	500	28.9	307	22.8
rs2395185																
GG	435	39.6	475	46.6	226	41.2	102	39.2	32	38.1	32	45.7	693	40.0	609	45.1
GT	515	46.9	440	43.2	258	47.0	126	48.5	39	46.4	33	47.1	812	46.9	599	44.4
TT	148	13.5	104	10.2	65	11.8	32	12.3	13	15.5	5	7.1	226	13.1	141	10.5
rs4488809 (rs4600802)																
TT	266	24.2	291	28.6	177	32.2	84	32.3	22	26.2	24	34.3	465	26.9	399	29.6
TC	506	46.1	500	49.1	274	49.9	130	50.0	44	52.4	41	58.6	824	47.6	671	49.7
CC	275	25.0	178	17.5	98	17.9	46	17.7	18	21.4	5	7.1	391	22.6	229	17.0
rs2736100																
TT	265	24.1	394	38.7	164	29.9	93	35.8	18	21.4	21	30.0	447	25.8	508	37.7
TG	592	53.9	481	47.2	271	49.4	123	47.3	46	54.8	42	60.0	909	52.5	646	47.9
GG	240	21.9	144	14.1	114	20.8	44	16.9	20	23.8	7	10.0	374	21.6	195	14.5

[a] Based on the median age of controls in all studies

Genetic data

The three FLCCA studies with HAP data were genotyped using Illumina 660 W arrays at either the NCI Core Genotyping Facility (CGF) (GELAC, SWHS) or Beijing Gene Square (GS) Inc. (SLCS) (Lan et al. 2012). The scanned intensity data from GS were collected and the genotypes were clustered and called at CGF using Illumina Genome Studio v2011.1 based on the GenTrain2 calling algorithm. Stringent quality control measures were used when building the final analytic GWAS dataset (Lan et al. 2012).

Gene–environmental interaction analyses

The analyses for interaction of genotype and HAP exposure were conducted using a Wald test under the Empirical Bayes estimation framework (Mukherjee and Chatterjee 2008). The Empirical Bayes estimator is a shrinkage

Table 2 Five GWAS-identified SNPs that confer risk of never-smoking lung cancer and gene–household air pollution interaction analyses by exposure type

SNP	Chromosome	Gene	All lung cancer cases ($n = 1{,}731$)	
			Solid fuel interaction	Coal interaction
			p value*	p value*
rs7086803	10	VTI1A	0.49	0.90
rs9387478	6	GOPC	**0.05**	0.35
rs2395185	6	*HLA Class II*	0.08	**0.02**
rs4488809[a]	3	*TP63*	0.07	**0.04**
rs2736100	5	TERT, hTERT	0.90	0.82

Bold highlights indicate $p \leq 0.05$

* Adjusted for age and study

[a] rs4488809 (rs4600802)

estimator which corresponds to a weighted average of the standard simple logistic regression estimator and the retrospective likelihood estimator (Chatterjee and Carroll 2005) under the assumption of gene–environment independence. This method has additional power relative to standard prospective logistic regression analysis of case–control data and provides superior control of type I error compared with retrospective methods including the case-only approach which are valid under the assumption of gene–environment independence. Our models included the main effects of the SNP and environmental exposure and their interaction term, as well as covariates for age (categorical) and study. To explore potential confounding by environmental tobacco smoke (ETS), we further adjusted our gene–HAP models by ETS (ever, never). We first restricted the analyses to our five a priori SNPs that achieved genome-wide significance level (i.e., $p \leq 10^{-8}$) in the GWAS: rs7086803, rs9387478,

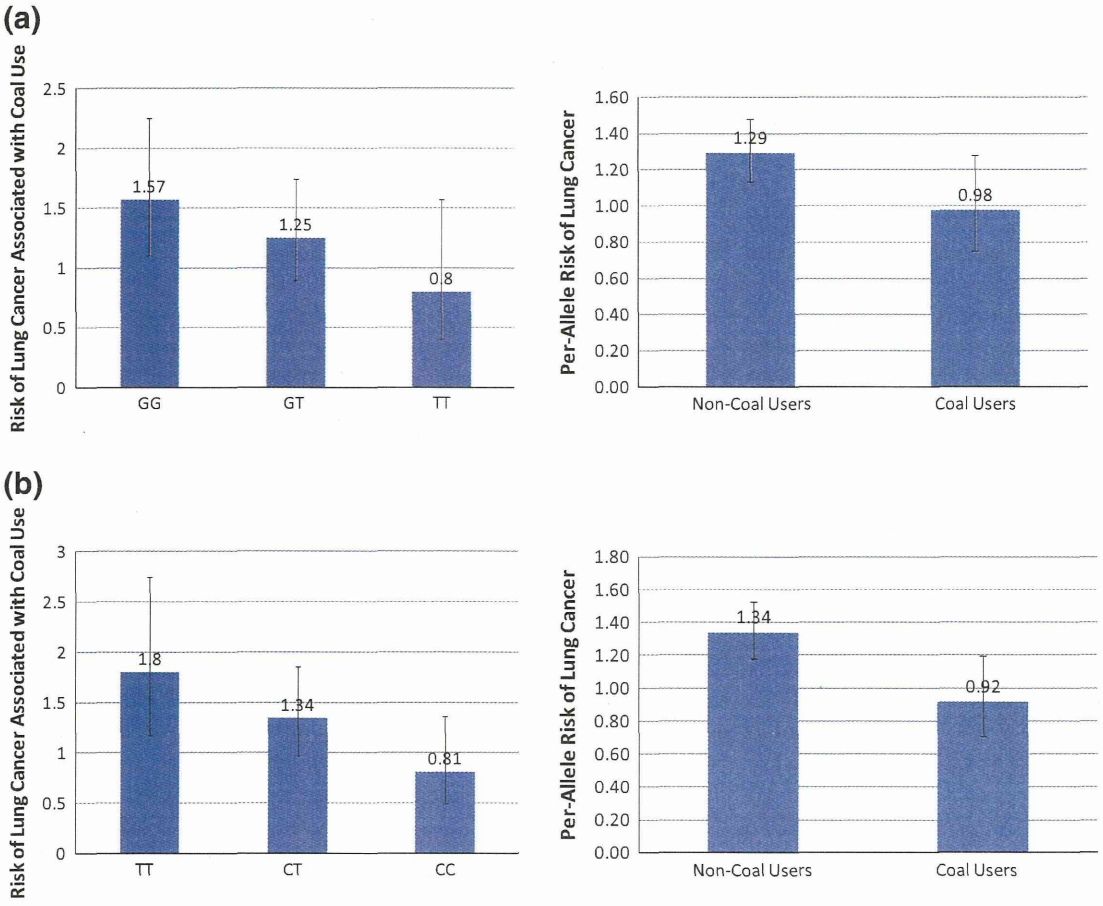

Fig. 1 Risk of lung cancer (odds ratio and 95 % confidence interval) associated with household coal use exposures stratified by the **a** rs2395185 and **b** rs4488809 (rs4600802) genotypes

rs2395185, rs4488809 (rs4600802) and rs2736100. Subsequent exploratory analyses were conducted using the full GWAS dataset.

Results

Genotype and HAP data from three studies in FLCCA, including a study conducted in Taiwan and two in mainland China, were pooled for a total of 1,731 never-smoking female lung cancer cases and 1,349 never-smoking female controls (Table 1). In all studies, we observed a 20 % increased risk of lung cancer associated with solid fuel use (OR 1.2; 95 % CI 1.0–1.4) and a 30 % increased risk of lung cancer associated with coal use (OR 1.3; 95 % CI 1.0–1.6). The risk of lung cancer associated with the five a priori SNPs in this analytic subset is summarized in Supplemental Table 1.

The gene–environment interactions between the five a priori SNPs that achieved genome-wide significance level (i.e., $p \leq 10^{-8}$) in our GWAS and our two metrics of HAP exposure are summarized in Table 2. For all lung cancers, 1 of the 5 SNPs was associated with a solid fuel use interaction ($p \leq 0.05$) (Table 2). Two of the 5 SNPs were associated with an interaction between coal use and lung cancer risk (rs2395185, $p = 0.02$; rs4488809 (rs4600802), $p = 0.04$). Further adjusting our gene–HAP models by ETS yielded similar results (Supplemental Table 2).The number of SNPs found to have statistically significant multiplicative interactions with coal use significantly exceeded the expected number of SNPs showing interaction [$p = 0.023$ for difference (2 of 5 SNPs vs 0.25 of 5 SNPs)]. The risk of lung cancer associated with coal exposure was found to vary with the respective rs2395185 and rs4488809 (rs4600802) alleles (Fig. 1). Dose–response relationships were observed between the lung cancer risk associated with coal use when stratifying by allele of these two SNPs. For both SNPs, the effect of the gene was strongest in those not exposed to coal (rs2395185: $OR_{per\text{-}allele} = 1.29$; 95 % CI 1.13–1.48; rs4488809 (rs4600802) $OR_{per\text{-}allele} = 1.34$; 95 % CI 1.18–1.53) (Fig. 1). Analyses using the full GWAS dataset did not yield any GWAS level significant interactions (i.e., $p \leq 10^{-8}$) with solid fuel or coal use (Supplemental Figure 1).

The gene–HAP results are presented in Supplemental Table 3 when restricted to only cases with lung adenocarcinoma and controls. Notably, genetic variation on chromosomes 6 (rs2395185) was associated with a coal interaction among adenocarcinomas ($p = 0.002$) (Supplemental Table 3). There was no evidence for interactions ($p > 0.05$) with rs7086803 and rs2736100 for all lung cancers or when restricting to adenocarcinomas.

Discussion

Lung cancer is the most common cancer in the world, with about 25 % of cases (53 % of those in women, 15 % of those in men) attributable to factors other than tobacco use (Parkin et al. 2005; Sun et al. 2007). Lung cancer in never smokers has unique genetic and etiologic risk factors when compared to lung cancer cases attributed to smoking tobacco (Subramanian and Govindan 2007; Lee et al. 2011). Women throughout Asia tend not to smoke, making them an ideal study population for elucidating the risk factors of never-smoking lung cancer. Smoke from domestic fuel (i.e., coal, wood, biomass) used for cooking and heating has been associated with lung cancer (Mumford et al. 1987; Hosgood et al. 2008; Lan et al. 2002, 2008; Hernandez-Garduno et al. 2004), particularly among Asian females using coal (Hosgood et al. 2010, 2011).

Consistent with the literature, we observed a 20 % increased risk of lung cancer associated with solid fuel use and a 30 % increased risk of lung cancer associated with coal use (Hosgood et al. 2010, 2011). Solid fuel combustion for heating and cooking increases the levels in the home of known carcinogens such as polycyclic aromatic hydrocarbons (PAHs) (Huang et al. 2011; Zhang and Smith 2003; Gustafson et al. 2007, 2008). Genetic variation that influences the metabolism of HAP constituents may identify susceptible populations. Initial explorations into genetic susceptibility to lung cancer attributed to HAP evaluated the interactions between (PAH-rich) smoky coal use and genetic variation in genes involved in metabolism and detoxification pathways of PAHs, such as glutathione S-transferase M1 (*GSTM1*). In Xuanwei, China where subjects experience some of the highest HAP exposures in the world, the *GSTM1* null genotype was associated with lung cancer risk, which was more pronounced among subjects with high levels of coal use relative to those with low coal use (Lan et al. 2000). Beyond the early *GSTM1* observations, for which there is some evidence of replication in additional populations with HAP exposures (Hosgood et al. 2007), genetic variation in *AKR1C3*, *OGG1*, and cell cycle genes have been suggested to play a role in lung cancer attributed to HAP (Lan et al. 2004; Hosgood et al. 2008). Here, we report additional gene–HAP interactions based on SNPs that were identified by GWAS.

We found that genetic variation in *HLA Class II* and *TP63* may be involved in gene–HAP interactions that are associated with lung cancer risk. Interestingly, we observed a per-allele dose–response relationship between the lung cancer risk associated when stratifying by allele of these two SNPs. These relationships suggest that the major allele is associated with higher risk of lung cancer in our populations. Further, we observed that the effect of the genotype was strongest in those not exposed to coal,

suggesting that these SNPs may play a greater role in the disease etiology of unexposed populations. Additional laboratory studies are needed to further determine the functionality of these SNPs and why the presence of the risk allele could lead to a protection from the adverse effects of HAP.

The roles played in human cell cycle and inflammation pathways by the proteins encoded by these three genes provided biological plausibility for our observed interactions; however, the evidence must be weighed in concert with the strengths and limitations of our study. For example, p63, the product of the *TP63* gene, is involved in the p53 pathway. p53 is critical to proper cell cycle regulation, and functions as a tumor suppressor in numerous cancers (Hernandez-Boussard et al. 1999). In addition, *TP63* genomic gains have been identified as potential indicators of pre-invasive lung lesions and early lung cancer diagnosis (Massion et al. 2009). Proteins coded by *HLA Class II* are both involved in the inflammation response. *HLA Class II* is involved in the regulation of lymphocytes necessary for B cell inflammatory responses. *HLA Class II* has both been shown to be involved in rheumatoid arthritis, a chronic inflammatory disease (van Gaalen et al. 2004). Interestingly, as a first line of defense against inhalation exposures, such as HAP, the respiratory tract releases cytokines (e.g., TNF-α, IL-1β) in response to site-specific inflammation (Moldoveanu et al. 2009). Therefore, our results suggest that HAP-induced lung cancer may be attributed to genetic variation in the cell cycle and inflammatory pathways. Although we are the first to report these specific gene–HAP interactions, previous studies have suggested interactions between additional cell cycle and inflammation genes and household coal use. Specifically, genetic variation in *PLA2G6*, *GSK3B*, *AKT1*, *EGF*, *TP53*, *PTEN*, *IL1B*, *IL8RA*, and, *IL12A* was associated with lung cancer risk in a rural Chinese population with substantial coal smoke exposures (Hosgood et al. 2008; Lee et al. 2007).

Our study is the largest study to date to evaluate gene–HAP interactions, and observed three novel gene–HAP interactions between exposures attributed to solid fuel use and genetic variation in *HLA Class II* and *TP63*. A major strength of our analysis is the use of never-smoking Asian female lung cancer cases and controls. Never smokers are the ideal population to evaluate environmental risk factors associated with lung cancer, since it minimizes the influence from tobacco smoking, the leading cause of lung cancer. Further, females in Asia experience some of the highest exposures from solid fuel burning. Further research is needed, however, to identify additional populations for confirmatory replication studies and to identify the underlying mechanism(s) of how in-home coal exposures interact with *HLA Class II* and *TP63*.

Acknowledgments This work was supported by the NCI intramural system. GELAC was supported in part by grants from the National Research Program for Biopharmaceuticals in Taiwan (MOHW103-TDU-PB-211-144003) and by Taiwan Bioinformatics Institute Core Facility (NSC 102-2319-B-400-001).

References

Amos CI, Wu XF, Broderick P, Gorlov IP, Gu J, Eisen T, Dong Q, Zhang Q, Gu XJ, Vijayakrishnan J, Sullivan K, Matakidou A, Wang YF, Mills G, Doheny K, Tsai YY, Chen WV, Shete S, Spitz MR, Houlston RS (2008) Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. Nat Genet 40:616–622

Chanock SJ, Hunter DJ (2008) Genomics—when the smoke clears. Nature 452:537–538

Chatterjee N, Carroll RJ (2005) Semiparametric maximum likelihood estimation exploiting gene-environment independence in case-control studies. Biometrika 92:399–418

Gustafson P, Barregard L, Strandberg B, Sallsten G (2007) The impact of domestic wood burning on personal, indoor and outdoor levels of 1,3-butadiene, benzene, formaldehyde and acetaldehyde. J Environ Monit 9:23–32

Gustafson P, Ostman C, Sallsten G (2008) Indoor levels of polycyclic aromatic hydrocarbons in homes with or without wood burning for heating. Environ Sci Technol 42:5074–5080

Hernandez-Boussard T, Rodriguez-Tome P, Montesano R, Hainaut P (1999) IARC p53 mutation database: a relational database to compile and analyze p53 mutations in human tumors and cell lines. International agency for research on cancer. Hum Mutat 14:1–8

Hernandez-Garduno E, Brauer M, Perez-Neria J, Vedal S (2004) Wood smoke exposure and lung adenocarcinoma in non-smoking Mexican women. Int J Tuberc Lung Dis 8:377–383

Hosgood HD III, Berndt SI, Lan Q (2007) GST genotypes and lung cancer susceptibility in Asian populations with indoor air pollution exposures: a meta-analysis. Mutat Res 636:134–143

Hosgood HD, Chapman R, Shen M, Blair A, Chen E, Zheng T, Lee KM, He X, Lan Q (2008a) Portable stove use is associated with lower lung cancer mortality risk in lifetime smoky coal users. Br J Cancer 99:1934–1939

Hosgood HD 3rd, Menashe I, Shen M, Yeager M, Yuenger J, Rajaraman P, He X, Chatterjee N, Caporaso NE, Zhu Y, Chanock SJ, Zheng T, Lan Q (2008b) Pathway-based evaluation of 380 candidate genes and lung cancer susceptibility suggests the importance of the cell cycle pathway. Carcinogenesis 29:1938–1943

Hosgood HD III, Boffetta P, Greenland S, Lee YCA, McLaughlin J, Seow A, Duell EJ, Andrew AS, Zaridze D, Szeszenia-Dabrowska N, Rudnai P, Lissowska J, Fabiánová E, Mates D, Bencko V, Foretova L, Janout V, Morgenstern H, Rothman N, Hung RJ, Brennan P, Lan Q (2010) In-home coal and wood use and lung cancer risk: a pooled analysis of the international lung cancer consortium. Environ Health Perspect 118:1743–1747

Hosgood HD 3rd, Wei H, Sapkota A, Choudhury I, Bruce N, Smith KR, Rothman N, Lan Q (2011) Household coal use and lung cancer: systematic review and meta-analysis of case-control studies, with an emphasis on geographic variation. Int J Epidemiol 40:719–728

Hsiung CA, Lan Q, Hong YC, Chen CJ, Hosgood HD, Chang IS, Chatterjee N, Brennan P, Wu C, Zheng W, Chang GC, Wu T, Park JY, Hsiao CF, Kim YH, Shen H, Seow A, Yeager M, Tsai YH, Kim YT, Chow WH, Guo H, Wang WC, Sung SW, Hu Z, Chen KY, Kim JH, Chen Y, Huang L, Lee KM, Lo YL, Gao YT, Kim JH, Liu L, Huang MS, Jung TH, Jin G, Caporaso N, Yu D, Kim

CH, Su WC, Shu XO, Xu P, Kim IS, Chen YM, Ma H, Shen M, Cha SI, Tan W, Chang CH, Sung JS, Zhang M, Yang TY, Park KH, Yuenger J, Wang CL, Ryu JS, Xiang Y, Deng Q, Hutchinson A, Kim JS, Cai Q, Landi MT, Yu CJ, Park JY, Tucker M, Hung JY, Lin CC, Perng RP, Boffetta P, Chen CY, Chen KC, Yang SY, Hu CY, Chang CK, Fraumeni JF, Jr., Chanock S, Yang PC, Rothman N, Lin D (2010) The 5p15.33 locus is associated with risk of lung adenocarcinoma in never-smoking females in Asia. PLoS Genet 6(8): e1001051

Huang S, Yang F, Zeng X, Chen J, Li R, Wen T, Li C, Wei W, Liu J, Chen L, Davis C, Xu J (2011) Preliminary characterization of the oral microbiota of Chinese adults with and without gingivitis. BMC Oral Health 11:33

Hung RJ, McKay JD, Gaborieau V, Boffetta P, Hashibe M, Zaridze D, Mukeria A, Szeszenia-Dabrowska N, Lissowska J, Rudnai P, Fabianova E, Mates D, Bencko V, Foretova L, Janout V, Chen C, Goodman G, Field JK, Liloglou T, Xinarianos G, Cassidy A, McLaughlin J, Liu G, Narod S, Krokan HE, Skorpen F, Elvestad MB, Hveem K, Vatten L, Linseisen J, Clavel-Chapelon F, Vineis P, Bueno-de-Mesquita HB, Lund E, Martinez C, Bingham S, Rasmuson T, Hainaut P, Riboli E, Ahrens W, Benhamou S, Lagiou P, Trichopoulos D, Holcatova I, Merletti F, Kjaerheim K, Agudo A, Macfarlane G, Talamini R, Simonato L, Lowry R, Conway DI, Znaor A, Healy C, Zelenika D, Boland A, Delepine M, Foglio M, Lechner D, Matsuda F, Blanche H, Gut I, Heath S, Lathrop M, Brennan P (2008) A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. Nature 452:633–637

IARC (2010) Household Use of Solid Fuels and High-temperature Frying (ed) Lyon: World Health Organization

Jou YS, Lo YL, Hsiao CF, Chang GC, Tsai YH, Su WC, Chen YM, Huang MS, Chen HL, Chen CJ, Yang PC, Hsiung CA (2009) Association of an EGFR intron 1 SNP with never-smoking female lung adenocarcinoma patients. Lung Cancer 64:251–256

Lan Q, He X, Costa DJ, Tian L, Rothman N, Hu G, Mumford JL (2000) Indoor coal combustion emissions, GSTM1 and GSTT1 genotypes, and lung cancer risk: a case–control study in Xuan Wei China. Cancer Epidemiol Biomark Prev 9:605–608

Lan Q, Chapman RS, Schreinemachers DM, Tian L, He X (2002) Household stove improvement and risk of lung cancer in Xuanwei China. J Natl Cancer Inst 94:826–835

Lan Q, Mumford JL, Shen M, Demarini DM, Bonner MR, He X, Yeager M, Welch R, Chanock S, Tian L, Chapman RS, Zheng T, Keohavong P, Caporaso N, Rothman N (2004) Oxidative damage-related genes AKR1C3 and OGG1 modulate risks for lung cancer due to exposure to PAH-rich coal combustion emissions. Carcinogenesis 25:2177–2181

Lan Q, He X, Shen M, Tian L, Liu LZ, Lai H, Chen W, Berndt SI, Hosgood HD, Lee KM, Zheng T, Blair A, Chapman RS (2008) Variation in lung cancer risk by smoky coal subtype in Xuanwei China. Int J Cancer 123:2164–2169

Lan Q, Hsiung CA, Matsuo K, Hong YC, Seow A, Wang Z, Hosgood HD 3rd, Chen K, Wang JC, Chatterjee N, Hu W, Wong MP, Zheng W, Caporaso N, Park JY, Chen CJ, Kim YH, Kim YT, Landi MT, Shen H, Lawrence C, Burdett L, Yeager M, Yuenger J, Jacobs KB, Chang IS, Mitsudomi T, Kim HN, Chang GC, Bassig BA, Tucker M, Wei F, Yin Z, Wu C, An SJ, Qian B, Lee VH, Lu D, Liu J, Jeon HS, Hsiao CF, Sung JS, Kim JH, Gao YT, Tsai YH, Jung YJ, Guo H, Hu Z, Hutchinson A, Wang WC, Klein R, Chung CC, Oh IJ, Chen KY, Berndt SI, He X, Wu W, Chang J, Zhang XC, Huang MS, Zheng H, Wang J, Zhao X, Li Y, Choi JE, Su WC, Park KH, Sung SW, Shu XO, Chen YM, Liu L, Kang CH, Hu L, Chen CH, Pao W, Kim YC, Yang TY, Xu J, Guan P, Tan W, Su J, Wang CL, Li H, Sihoe AD, Zhao Z, Chen Y, Choi YY, Hung JY, Kim JS, Yoon HI, Cai Q, Lin CC, Park IK, Xu P, Dong J, Kim C, He Q, Perng RP, Kohno T, Kweon SS et al (2012) Genome-wide association analysis identifies new lung cancer susceptibility loci in never-smoking women in Asia. Nat Genet 44:1330–1335

Landi MT, Chatterjee N, Yu K, Goldin LR, Goldstein AM, Rotunno M, Mirabello L, Jacobs K, Wheeler W, Yeager M, Bergen AW, Li Q, Consonni D, Pesatori AC, Wacholder S, Thun M, Diver R, Oken M, Virtamo J, Albanes D, Wang Z, Burdette L, Doheny KF, Pugh EW, Laurie C, Brennan P, Hung R, Gaborieau V, McKay JD, Lathrop M, McLaughlin J, Wang Y, Tsao MS, Spitz MR, Wang Y, Krokan H, Vatten L, Skorpen F, Arnesen E, Benhamou S, Bouchard C, Metspalu A, Vooder T, Nelis M, Valk K, Field JK, Chen C, Goodman G, Sulem P, Thorleifsson G, Rafnar T, Eisen T, Sauter W, Rosenberger A, Bickeboller H, Risch A, Chang-Claude J, Wichmann HE, Stefansson K, Houlston R, Amos CI, Fraumeni JF Jr, Savage SA, Bertazzi PA, Tucker MA, Chanock S, Caporaso NE (2009) A genome-wide association study of lung cancer identifies a region of chromosome 5p15 associated with risk for adenocarcinoma. Am J Hum Genet 85:679–691

Lee KM, Shen M, Chapman RS, Yeager M, Welch R, He X, Zheng T, Hosgood HD, Yang D, Berndt SI, Chanock S, Lan Q (2007) Polymorphisms in immunoregulatory genes, smoky coal exposure and lung cancer risk in Xuan Wei China. Carcinogenesis 28:1437–1441

Lee YJ, Kim JH, Kim SK, Ha SJ, Mok TS, Mitsudomi T, Cho BC (2011) Lung cancer in never smokers: change of a mindset in the molecular era. Lung Cancer 72:9–15

Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M, Atkinson C, Bacchus LJ, Bahalim AN, Balakrishnan K, Balmes J, Barker-Collo S, Baxter A, Bell ML, Blore JD, Blyth F, Bonner C, Borges G, Bourne R, Boussinesq M, Brauer M, Brooks P, Bruce NG, Brunekreef B, Bryan-Hancock C, Bucello C, Buchbinder R, Bull F, Burnett RT, Byers TE, Calabria B, Carapetis J, Carnahan E, Chafe Z, Charlson F, Chen H, Chen JS, Cheng AT, Child JC, Cohen A, Colson KE, Cowie BC, Darby S, Darling S, Davis A, Degenhardt L, Dentener F, Des Jarlais DC, Devries K, Dherani M, Ding EL, Dorsey ER, Driscoll T, Edmond K, Ali SE, Engell RE, Erwin PJ, Fahimi S, Falder G, Farzadfar F, Ferrari A, Finucane MM, Flaxman S, Fowkes FG, Freedman G, Freeman MK, Gakidou E, Ghosh S, Giovannucci E, Gmel G, Graham K, Grainger R, Grant B, Gunnell D, Gutierrez HR, Hall W, Hoek HW, Hogan A, Hosgood HD, Hoy D, Hu H, Hubbell BJ, Hutchings SJ, Ibeanusi SE, Jacklyn GL, Jasrasaria R, Jonas JB, Kan H, Kanis JA, Kassebaum N, Kawakami N, Khang YH, Khatibzadeh S, Khoo JP, Kok C, Laden F (2013) A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380:2224–2260

Massion PP, Zou Y, Uner H, Kiatsimkul P, Wolf HJ, Baron AE, Byers T, Jonsson S, Lam S, Hirsch FR, Miller YE, Franklin WA, Varella-Garcia M (2009) Recurrent genomic gains in preinvasive lesions as a biomarker of risk for lung cancer. PLoS ONE 4:e5611

Moldoveanu B, Otmishi P, Jani P, Walker J, Sarmiento X, Guardiola J, Saad M, Yu J (2009) Inflammatory mechanisms in the lung. J Inflamm Res 2:1–11

Mukherjee B, Chatterjee N (2008) Exploiting gene-environment independence for analysis of case-control studies: an empirical Bayes-type shrinkage estimator to trade-off between bias and efficiency. Biometrics 64:685–694

Mumford JL, He XZ, Chapman RS, Cao SR, Harris DB, Li XM, Xian YL, Jiang WZ, Xu CW, Chuang JC et al (1987) Lung cancer and indoor air pollution in Xuan Wei China. Science 235:217–220

Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55:74–108

Subramanian J, Govindan R (2007) Lung cancer in never smokers: a review. J Clin Oncol 25:561–570

Sun S, Schiller JH, Gazdar AF (2007) Lung cancer in never smokers—a different disease. Nat Rev Cancer 7:778–790

Truong T, Hung RJ, Amos CI, Wu X, Bickeboller H, Rosenberger A, Sauter W, Illig T, Wichmann HE, Risch A, Dienemann H, Kaaks R, Yang P, Jiang R, Wiencke JK, Wrensch M, Hansen H, Kelsey KT, Matsuo K, Tajima K, Schwartz AG, Wenzlaff A, Seow A, Ying C, Staratschek-Jox A, Nurnberg P, Stoelben E, Wolf J, Lazarus P, Muscat JE, Gallagher CJ, Zienolddiny S, Haugen A, van der Heijden HF, Kiemeney LA, Isla D, Mayordomo JI, Rafnar T, Stefansson K, Zhang ZF, Chang SC, Kim JH, Hong YC, Duell EJ, Andrew AS, Lejbkowicz F, Rennert G, Muller H, Brenner H, Le Marchand L, Benhamou S, Bouchardy C, Teare MD, Xue X, McLaughlin J, Liu G, McKay JD, Brennan P, Spitz MR (2010) Replication of lung cancer susceptibility loci at chromosomes 15q25, 5p15, and 6p21: a pooled analysis from the International Lung Cancer Consortium. J Natl Cancer Inst 102:959–971

van Gaalen FA, van Aken J, Huizinga TW, Schreuder GM, Breedveld FC, Zanelli E, van Venrooij WJ, Verweij CL, Toes RE, de Vries RR (2004) Association between *HLA Class II* genes and autoantibodies to cyclic citrullinated peptides (CCPs) influences the severity of rheumatoid arthritis. Arthritis Rheum 50:2113–2121

Wang Y, Broderick P, Webb E, Wu X, Vijayakrishnan J, Matakidou A, Qureshi M, Dong Q, Gu X, Chen WV, Spitz MR, Eisen T, Amos CI, Houlston RS (2008) Common 5p15.33 and 6p21.33 variants influence lung cancer risk. Nat Genet 40:1407–1409

Wu C, Hu Z, Yu D, Huang L, Jin G, Liang J, Guo H, Tan W, Zhang M, Qian J, Lu D, Wu T, Lin D, Shen H (2009) Genetic variants on chromosome 15q25 associated with lung cancer risk in Chinese populations. Cancer Res 69:5065–5072

Yin Z, Su M, Li X, Li M, Ma R, He Q, Zhou B (2009) ERCC2, ERCC1 polymorphisms and haplotypes, cooking oil fume and lung adenocarcinoma risk in Chinese non-smoking females. J Exp Clin Cancer Res 28:153

Zhang J, Smith KR (2003) Indoor air pollution: a global health concern. Br Med Bull 68:209–225

Zhang Y, Shu XO, Gao YT, Ji BT, Yang G, Li HL, Kilfoy B, Rothman N, Zheng W, Chow WH (2007) Family history of cancer and risk of lung cancer among nonsmoking Chinese women. Cancer Epidemiol Biomark Prev 16:2432–2435

Zheng W, Chow WH, Yang G, Jin F, Rothman N, Blair A, Li HL, Wen W, Ji BT, Li Q, Shu XO, Gao YT (2005) The Shanghai Women's Health Study: rationale, study design, and baseline characteristics. Am J Epidemiol 162:1123–1131

KOKUYO セホ-50B