Published in final edited form as:
Lancet Oncol. 2010 August ; 11(8): 714–716. doi:10.1016/S1470-2045(10)70096-6.

GPC5 rs2352028 variant and risk of lung cancer in never smokers

Maria Teresa Landi, MD[1,*], **Nilanjan Chatterjee, PhD**[1], **Neil E. Caporaso, MD**[1], **Melissa Rotunno, MD**[1], **Demetrius Albanes, MD**[1], **Michael Thun, MD**[2], **William Wheeler, PhD**[3], **Albert Rosenberger, PhD**[4], **Heike Bickeböller, PhD**[4], **Angela Risch, PhD**[5], **Yufei Wang, PhD**[6], **Valerie Gaborieau, MS**[7], **Thorgeir Thorgeirsson, PhD**[8], **Daniel Gudbjartsson, PhD**[8], **Patrick Sulem, MD**[8], **Margaret R. Spitz, MD**[9], **H.-Erich Wichmann, MD**[10,11], **Thorunn Rafnar, PhD**[8], **Kari Stefansson, MD, PhD**[8], **Richard S. Houlston, PhD**[6], and **Paul Brennan, PhD**[7]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, MD, 20892, USA [2]American Cancer Society; Epidemiology and Surveillance Research; Atlanta, GA, 30301; USA [3]Information Management Services, Inc.; Rockville, MD, 20852; USA [4]Department of Genetic Epidemiology, Medical School, Georg-August-University Göttingen [5]Division of Epigenetics and Cancer Risk Factors, German Cancer Research Center, Heidelberg, Germany [6]Section of Cancer Genetics; Institute of Cancer Research; Surrey, SM2 5NG; UK [7]International Agency for Research on Cancer; Lyon, France, 69372; France [8]deCODE Genetics; Reykjavik, 101; Iceland [9]Department of Epidemiology, M.D. Anderson Cancer Center; University of Texas; Houston, TX 77030; USA [10]Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany [11]Institute of Medical Informatics, Biometry and Epidemiology, Chair of Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany

We read with great interest the genome-wide association study (GWAS) of Li *et al.*[1] in the April, 2010 issue of *The Lancet Oncology*, reporting an association (OR=1·46, 95%CI=1·26–1·70) between the single nucleotide polymorphism rs2352028 mapping to chromosome 13q31·3 and lung cancer risk in never smokers. We sought to replicate this finding using data from seven GWAS of lung cancer in Caucasian populations,[2–5] with rs2352028 genotype data on 754 never smoker lung cancer cases and 10,580 controls. None of the seven studies provided statistically significant evidence for an association between rs2352028 and lung cancer risk in never smokers, even when combined (P=0·57, under both fixed and random effects models; Cochran's Q $P_{heterogeneity}$=0·62, Figure 1), although we had >90% statistical power to detect an association with rs2352028 of 1·26 (the lower limit of the 95% CI reported by Li *et al.*) at the 5% significance level. Moreover, the association was not significant in the overall meta-analysis pooling results from our seven studies and

[*]Corresponding author: Maria Teresa Landi, MD, PhD, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, 6120 executive Blvd., EPS 7114, Bethesda, MD 20892-7236, USA, Phone: (001) 301-402-9519, Fax: (001) 301-402-4489, landim@mail.nih.gov.

Authors' contributions

Drs. Landi, Brennan, Caporaso, Houlston and Spitz designed the study; Drs. Chatterjee and Wheeler conducted the meta-analyses; Dr. Rotunno conducted the gene expression analysis; Dr. Landi wrote the manuscript; each author analyzed data from their own Institution, provided results for the summary meta-analysis, participated in data interpretation and reviewed the final manuscript.

Conflicts of interest

Dr. Kari Stefansson and his team (Drs. Thorunn Rafnar, Patrick Sulem, Thorgeir Thorgeirsson, and Daniel Gudbjartsson) are shareholders of the deCODE Genetics company. No other authors have conflicts of interest to declare.

Ethics committee approval

Each participating study received ethics approval from their respective Institutional Review Boards

from Li *et al.* (OR=1·10, P=0·25, under random effects model; $P_{heterogeneity}$=0·003). Analyses using other genetic models (Supplemental Figure 1); adjusting for additional potential confounders, including history of COPD, exposure to second-hand smoke and family history of lung cancer (EAGLE[2] only, OR=0·86; 96% CI = 0·63–1·19, p=0·37); or restricted to adenocarcinomas (Figure 1) also provided no evidence for a significant relationship. Of note, all controls in our analyses were never smokers, with the exception of the UK sample for which we had no smoking information. However, the frequency of the rs2352028 T allele was not significantly different between ever smokers (19,656) and never smokers (7,453) (OR=1·04, p-value=0·30) from other groups, thus the results are not likely to be affected by smoking status in controls.

The Li *et al.* GWAS was based on 888 cases and 1,384 controls and the association between rs2352028 and lung cancer was at P-value=$5{\cdot}94\times10^{-6}$. While nominally significant, it is well recognized that as GWAS involve many markers, numerous false positive associations will inevitably be generated, with only a small number being truly associated with disease susceptibility. Hence, associations require a high level of statistical significance ($5{\cdot}0\times10^{-7}$–$5{\cdot}0\times10^{-8}$) to be established beyond reasonable doubt, and the reported association does not attain genome-wide significance. Moreover, under a random effects model the association between rs2352028 and lung cancer reported by Li *et al.* is weak (P=0·0027 overall and P=0·034 for adenocarcinomas). The significant heterogeneity between our studies and those from Li *et al.* could be due to genuine differences in underlying population characteristics and/or due to "winner's curse" associated with a chance finding.

Li *et al.* reported a relationship between *GPC5* expression in 70 non-tumor lung tissue samples and rs2352028 genotype. We examined this correlation in fresh frozen lung tissue samples from 45 adenocarcinomas and 37 non-tumor samples[6] and in blood samples from 62 adenocarcinoma cases and 77 controls. Although we found lower expression levels in tumor tissue *vs.* noninvolved tissue as previously reported[1], we found no significant correlation of rs2352028 genotypes with *GPC5* expression in the lung tumor and non-involved tissue samples from cases and in blood samples from controls (p-values=0·07, 0·32 and 0·41, respectively). We observed an association (p=0·03) between genotype and *GPC5* expression in blood samples from adenocarcinoma cases, although no trend was apparent and no difference in *GPC5* expression between cases and controls was observed (Supplemental Figure 2).

This work highlights the importance of large sample sizes and the need for replication in multiple independent groups to identify true positive associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding sorce

This work was supported by the Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH. The funding source had no role in study design, data collection, analysis, data interpretation, writing the report or decision to submit the paper.

Reference List

1. Li Y, Sheu CC, Ye Y, et al. Genetic variants and risk of lung cancer in never smokers: a genome-wide association study. Lancet Oncol. 2010; 11:321–330. [PubMed: 20304703]

2. Landi MT, Chatterjee N, Yu K, et al. A genome-wide association study of lung cancer identifies a region of chromosome 5p15 associated with risk for adenocarcinoma. Am J Hum Genet. 2009; 85:679–691. [PubMed: 19836008]

3. Hung RJ, McKay JD, Gaborieau V, et al. A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. Nature. 2008; 452:633–637. [PubMed: 18385738]

4. Wang Y, Broderick P, Webb E, et al. Common 5p15.33 and 6p21.33 variants influence lung cancer risk. Nat Genet. 2008; 40:1407–1409. [PubMed: 18978787]

5. Thorgeirsson TE, Geller F, Sulem P, et al. A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. Nature. 2008; 452:638–642. [PubMed: 18385739]

6. Landi MT, Dracheva T, Rotunno M, et al. Gene expression signature of cigarette smoking and its role in lung adenocarcinoma development and survival. PLoS ONE. 2008; 3:e1651. [PubMed: 18297132]

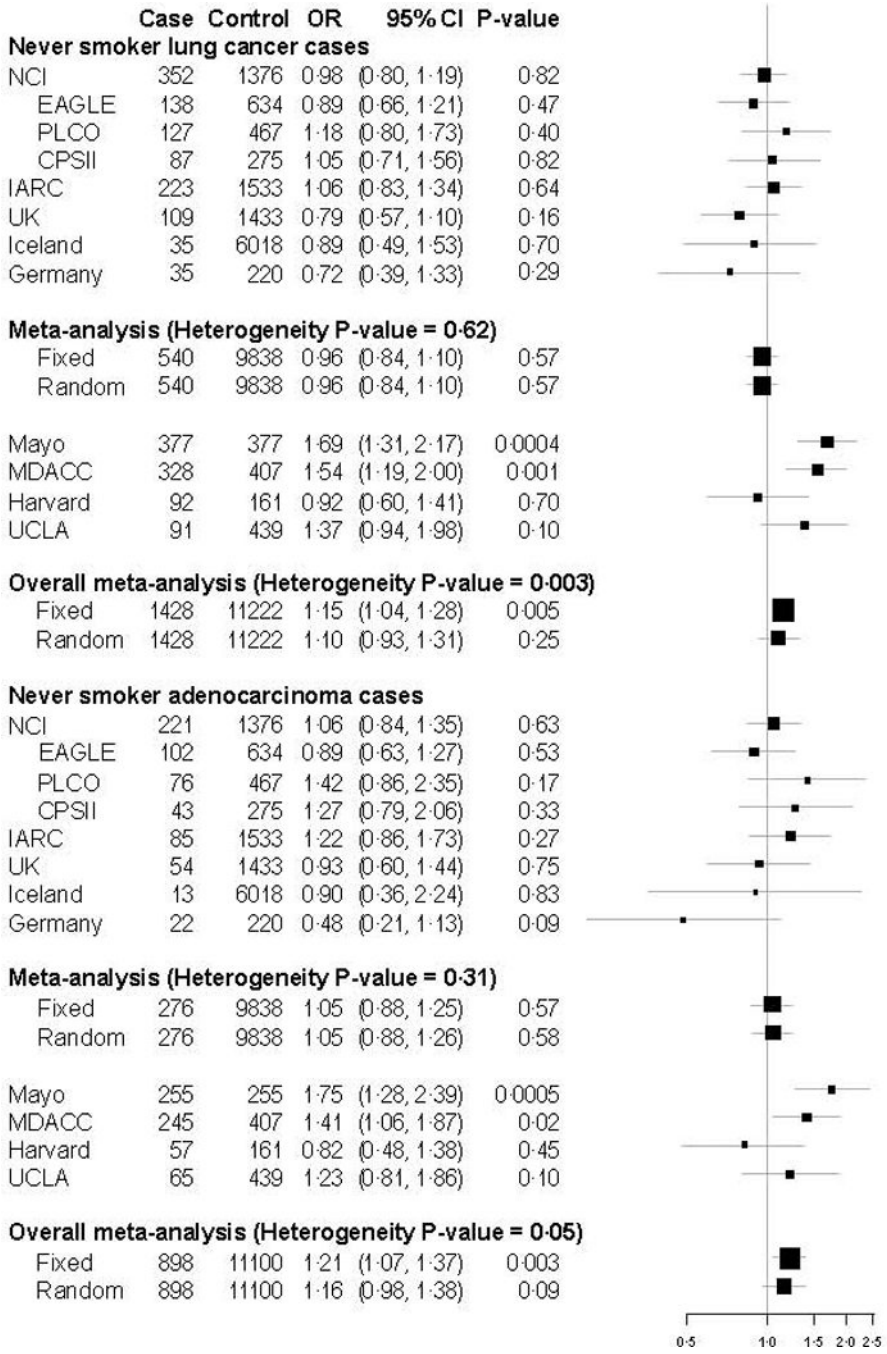

Figure 1.

Association between rs2352028 and lung cancer risk overall and in adenocarcinoma only in never smokers (additive genetic model). Results from seven independent studies and overall meta-analysis including results from the new seven independent studies plus four previously reported[1] studies are shown. EAGLE, Environment And Genetics in Lung cancer Etiology;[2] PLCO, Prostate Lung Colon Ovary Screening Trial;[2] CPS-II, Cancer Prevention Study II Nutrition;[2] IARC, International Agency for Research on Cancer;[3] UK, Institute of Cancer Research;[4] Iceland, deCODE Genetics;[5] Germany, HGF lung cancer study.[2] Black squares indicate the odds ratios, with the size of the square inversely proportional to its variance. Horizontal lines represent 95% CI. The vertical line shows the value for no effect (odds ratio

=1·0). The random effects model and test for heterogeneity was conducted with the R function “mima”; the forest plot was conducted using the R package “rmeta”.