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Author Contributions

AS	Study design, composed manuscript
AG	Study design, composed manuscript
AH	Study design, composed manuscript
AT	Study design, composed manuscript
BS	Study design, composed manuscript
BZ	Study design, composed manuscript, co-supervised the study
BH	Study design, composed manuscript
BQ	Study design, composed manuscript
BAB	Study design, composed manuscript
BTJ	Study design, composed manuscript
CAH	Study design, composed manuscript
CCC	Study design, composed manuscript
CW	Study design, composed manuscript
CLW	Study design, composed manuscript
CYC	Study design, composed manuscript
CFH	Study design, composed manuscript
CJY	Study design, composed manuscript
CHC	Study design, composed manuscript
CNM	Study design, composed manuscript
DL	Study design, composed manuscript
DL	Study design, composed manuscript, co-supervised the study
FYT	Study design, composed manuscript
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HDH	Study design, composed manuscript
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HZ	Performed analyses, composed manuscript
HN	Study design, composed manuscript
HNK	Study design, composed manuscript
HI	Study design, composed manuscript
HK	Study design, composed manuscript
HS	Study design, composed manuscript
HIY	Study design, composed manuscript

Tuberculosis Infection and Lung Adenocarcinoma: Mendelian

HZ	Study design, composed manuscript
HS	Study design, composed manuscript, co-supervised the study
HM	Study design, composed manuscript
HC	Study design, composed manuscript
HG	Study design, composed manuscript
HLC	Study design, composed manuscript
HSJ	Study design, composed manuscript
IKP	Study design, composed manuscript
IJO	Study design, composed manuscript
ISC	Study design, composed manuscript
IALO	Study design, composed manuscript
JSS	Study design, composed manuscript
JYP	Study design, composed manuscript
JCMH	Study design, composed manuscript
JYYW	Composed manuscript, study design, performed analyses
JS	Study design, composed manuscript
JC	Study design, composed manuscript
JL	Study design, composed manuscript
JS	Study design, composed manuscript
JL	Study design, composed manuscript
JL	Study design, composed manuscript
JEC	Study design, composed manuscript
JHK	Study design, composed manuscript
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KS	Study design, composed manuscript
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KS	Study design, composed manuscript
KYC	Study design, composed manuscript

Randomization and Pathway Analysis of Genome-wide

KHP	Study design, composed manuscript
KA	Study design, composed manuscript
LPC	Study design, composed manuscript
LB	Study design, composed manuscript
LJ	Study design, composed manuscript
LL	Study design, composed manuscript
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NEC	Study design, composed manuscript
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PCY	Study design, composed manuscript, co-supervised the study
PG	Study design, composed manuscript
PC	Study design, composed manuscript
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QL	Study design, composed manuscript, co-supervised the study
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TH	Study design, composed manuscript

Association Study Data from Never-Smoking Asian Women

TW	Study design, composed manuscript, co-supervised the study
TM	Study design, composed manuscript
TYC	Study design, composed manuscript
VLS	Study design, composed manuscript
WSH	Study design, composed manuscript
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WJS	Study design, composed manuscript
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WZ	Study design, composed manuscript
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YTG	Study design, composed manuscript
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ZH	Study design, composed manuscript
ZY	Study design, composed manuscript

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Abstract

We investigated whether genetic susceptibility to tuberculosis (TB) influences lung adenocarcinoma development among never-smokers using TB genome-wide association study (GWAS) results within the Female Lung Cancer Consortium in Asia. Pathway analysis with the adaptive rank truncated product method was used to assess the association between a TB-related gene-set and lung adenocarcinoma using GWAS data from 5,512 lung adenocarcinoma cases and 6,277 controls. The gene-set consisted of 31 genes containing known/suggestive associations with genetic variants from previous TB-GWAS. Subsequently, we followed-up with Mendelian Randomization to evaluate the association between TB and lung adenocarcinoma using three genome-wide significant variants from previous TB-GWAS in East Asians. The TB-related gene-set was associated with lung adenocarcinoma (p=0.016). Additionally, the Mendelian Randomization showed an association between TB and lung adenocarcinoma (OR=1.31, 95% CI: 1.03, 1.66, p=0.027). Our findings support TB as a causal risk factor for lung cancer development among never-smoking Asian women.

LR	Study design, composed manuscript
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XH	Study design, composed manuscript
KML	Study design, composed manuscript
BB	Study design, composed manuscript
TYY	Study design, composed manuscript
YJL	Study design, composed manuscript
RPP	Study design, composed manuscript
KCC	Study design, composed manuscript
JYH	Study design, composed manuscript
CCL	Study design, composed manuscript
CJC	Study design, composed manuscript
HCL	Study design, composed manuscript
MKYH	Study design, composed manuscript
HMHP	Study design, composed manuscript
KYS	Study design, composed manuscript
JH	Study design, composed manuscript

†These authors contributed equally.
‡These authors co-supervised the work.

Keywords

Tuberculosis; lung cancer; lung adenocarcinoma; Mendelian Randomization; Pathway Analysis

Introduction

Lung cancer is a substantial health burden worldwide that accounted for nearly 1.76 million deaths in 2018 [1]. Smoking is the most common cause of lung cancer; however, an estimated 25% of lung cancer patients worldwide are never-smokers [2]. Among never-smokers, overall incidence rates of 14.4-20.8 lung cancer cases per 100,000 person-years were estimated for women and 4.8-13.7 cases per 100,000 person-years for men [3, 4]. Asian women have among the highest incidence rates of lung cancer in the world among never-smokers [2, 5]. The complex etiology underlying this malignancy in this population remains unclear; however, various factors including infections [6–9] are suspected to contribute to this excess.

A previous genome-wide association study (GWAS) identified multiple genetic loci, including those on chromosomes 3q28, 5p15.33, 6p21.1, 6p21.32, 6q22.2, 9p21.3, 10q25.2 and 12q13.13 [8–10], that contribute to increased lung adenocarcinoma risk among never-smoking women. Although genomic studies have begun to shed light onto the genetic underpinnings of lung cancer etiology, genetic variants from GWAS in total only explain an estimated 12% of the heritability of lung cancer risk to date [11]. This issue is further compounded by the stringent correction for multiple comparisons that has become convention in GWAS. As a result, many susceptibility genes that potentially contribute to lung cancer development are likely to remain unidentified in GWAS of never-smoking Asian women based on sample sizes used to date. Pathway analysis (also known as gene set analysis) is a powerful method that complements existing GWAS by analyzing pre-defned groups of genes or biological pathways enriched with genetic variants that could potentially be associated with complex diseases [12]. When applied to existing GWAS data, pathway analysis may discover associations that could not be detected by conventional single-marker analyses, in addition to providing the added value of cogent biologic interpretation to GWAS findings.

Pulmonary tuberculosis (TB) is a common respiratory disease found throughout low and middle income countries in Asia that has been reported as a potential risk factor for lung cancer development [6]. Pulmonary TB is a communicable disease that is caused by infection with *Mycobacterium tuberculosis* (Mtb), a species of pathogenic bacteria that is spread and contracted through contaminated airborne droplets [13]. The symptoms of TB include severe persistent coughing, hemoptysis, chest pain, fever, and weight loss [13]. TB infection may contribute to increased lung cancer risk through biological mechanisms involving prolonged pulmonary inflammation leading to tissue damage, fibrosis, scar formation, and genomic damage [14–16]. Various human studies found a link between pulmonary TB and lung cancer [6, 14, 17–21]; however, several studies did not detect an association [22–26]. As such, the relationship between TB and lung cancer has not been firmly established.

To further investigate the relationship between TB and lung cancer, we analyzed data from previous GWAS of TB within the Female Lung Cancer Consortium in Asia (FLCCA), the largest GWAS of never-smoking women ever conducted to date. A pathway analysis was conducted to determine whether genetic factors related to TB also contribute to lung adenocarcinoma development. We followed-up with Mendelian Randomization (MR) to evaluate the potential association between TB infection and lung adenocarcinoma. Findings from our study may contribute to confirming a link between these respiratory diseases and to the understanding of the biological mechanism underlying lung carcinogenesis independent of cigarette smoking.

Methods

Study sample and GWAS

We evaluated GWAS data from 5,512 lung adenocarcinoma cases and 6,277 cancer-free controls from the Female Lung Cancer Consortium in Asia (FLCCA) [9]. All participating studies provided individual genotype data except for the Nanjing study [27], the Japanese Lung Cancer Collaborative Study (JLCCS) [28], and another Japanese study [29]. These three studies provided summary data instead. Details of the participating studies including the genotyping process, quality control procedures, and statistical methods to generate summary data from the meta-analysis were previously described [8–10, 27–29]. GWAS data are available at dbGAP (https://www.ncbi.nlm.nih.gov/gap, study accession: phs000716.v1.p1). Briefly, the participants were never-smoking adult Asian women who resided in Mainland China, Hong Kong, Singapore, Taiwan, South Korea, and Japan at the time of recruitment (Supplementary Table 1). Nearly all the samples were genotyped using Illumina 660W and 610K SNP microarrays as previously described [9, 27–29]. Unconditional logistic regression models were used to estimate the odds ratios (OR) and 95% confidence intervals (CI) for the additive trend effects of each SNP (with 1-degree of freedom) on lung adenocarcinoma risk, adjusted for study center, age, and the top three eigenvectors. Summary statistics were generated and used for the subsequent pathway analysis.

Pathway analysis

Pathway analysis was conducted using the summary statistics-based adaptive rank truncated product (sARTP) method, which combines SNP-level association statistics across variants in a gene-set [12]. The sARTP method also used a model selection procedure to identify a subset of genes and SNPs that contributed the most to the overall association. Only genotyped SNPs in the lung adenocarcinoma dataset were analyzed because imputed SNPs in linkage disequilibrium (LD) with genotyped SNPs do not add more information to the pathway analysis. The association signals from up to five SNPs in a gene were adaptively accumulated. The sARTP method adjusts for the number of SNPs in a gene and number of genes in a pathway through a resampling procedure to control for false-positives. The gene- and pathway-level association p-values were estimated from the resampled null distribution using 10 million resampling steps.

A set of 31 TB-related genes was compiled using a lower threshold for known or suggestive single nucleotide polymorphism (SNP) associations with TB from GWAS that were conducted around the world [30–39]. Specifically, genes from each study were chosen if they contained at least one SNP in exons or introns that was associated with TB at a threshold of $p<5.0 \times 10^{-6}$ to maximize sensitivity for data exploration. We mapped SNPs 20 kb upstream and downstream of each gene. We integrated *a priori* knowledge from previous GWAS conducted around the world when creating the TB gene-set to determine if a trans-ethnic effect exists in the TB-lung cancer association. Using a TB gene-set defined by European and African populations should not result in biased results because the GWAS data used to identify those TB-genes are independent of the data used in our own association analysis.

Pathway analysis based on summary data requires a set of samples with individual genotype data as the reference panel from which the LD between SNPs is estimated. As we only had summary data from the Nanjing study and the two studies from Japan, a reference dataset consisting of 1000 subjects based on individual genotype data in the FLCCA study was created. We performed stratified sampling in cases and controls by oversampling subjects from mainland China and Japan to mimic the genetic pattern in the pooled sample that was comprised of subjects who were scanned across all study centers (Supplementary Table 2, Supplementary Figure 1A/B).

Functional annotation

We used the Database for Annotation, Visualization and Integrated Discovery (DAVID) v6.8 (https://david.ncifcrf.gov) and GeneCards – Human Gene Database (https://www.genecards.org/) to explore the biological themes of contributing genes with $P_{gene}<0.05$ [40].

Mendelian Randomization

To follow-up on the pathway analysis and generate further evidence for a TB-lung cancer link, we conducted MR as previously described [41] to evaluate a possible causal association between TB and lung adenocarcinoma among never-smoking women. MR is a special form of instrumental variable analysis to determine the causal relationship between an exposure or phenotype and an outcome, even in the presence of unmeasured confounding [41]. Estimation of this potential causal effect is accomplished by mimicking the causal structure of a randomized clinical trial [42–45]. MR uses genetic variants as instrumental variables for modifiable risk factors (i.e. TB infection/susceptibility) that affect a health outcome (i.e., lung adenocarcinoma). Although there are various required conditions [46], the main assumption of MR analysis is that the genetic instrument only affects the outcome through its direct association with the modifiable risk factor. Given that the participants of FLCC A were predominantly of East Asian ancestry, genome-wide significant SNPs that were previously found to be associated with TB in genomic studies of East Asians [35, 47] were used as instruments in our analysis. These SNPs included rs4240897 [35], rs2269497 [35], and rs9272461 [47]. P-values <0.05 for each analysis were considered statistically noteworthy.

This was an observational study and no experiments were conducted on humans. All methods were performed in accordance with relevant guidelines and regulations of the National Institutes of Health and all the participating institutions. Institutional Review Board approval from The Central Institutional Review Board for the National Cancer Institute and all the other study sites, in addition to written informed consent from all research participants were obtained.

Results

Pathway analysis

The overall TB-related gene-set was associated with lung adenocarcinoma ($p_{pathway}$=0.016) among never-smoking Asian women. Four genes were selected by the sARTP method as having the greatest contribution to the association. These genes included forkhead associated phosphopeptide binding domain 1 (FHAD1, p=0.001), zinc finger protein FOG family member 2 (ZFPM2, p=0.020), major histocompatibility complex class (MHC) II DQ alpha 1 (HLA-DQA1, p=0.009), and discs large MAGUK scaffold protein 2 (DLG2, p=0.017) (Table 1, Supplementary Table 3).

Mendelian Randomization

There have been a number of large-scale GWAS of pulmonary TB conducted in populations of European ancestry [31, 37]. However, only a few TB GWAS have been conducted in East Asians. From these studies, we identified four independent genome-wide significant variants associated with TB in East Asians, three of which were in our dataset (i.e., rs4240897 [35], rs2269497 [35], and rs9272461 [47]). We conducted MR using the three TB-related SNPs and found that the estimated causal effect of TB on lung adenocarcinoma was statistically noteworthy (OR_{MR}=1.31, 95% CI: 1.03, 1.66, p=0.027). Among these SNPs, the rs4240897G>A variant of the Mitofusin 2 (MFN2) gene was inversely associated with lung adenocarcinoma risk (OR=0.92, 95% CI: 0.86-0.98, p=5.5E-03) and with TB [35].

Discussion

In the largest GWAS of lung cancer among female never-smokers in the world, we applied genomic methods to investigate the relationship between TB infection, TB-related genes, and lung adenocarcinoma. First, we conducted a pathway analysis to evaluate whether genetic factors that refect biologic processes of TB also contribute to lung cancer development. The TB-related gene-set was found to be associated with lung adenocarcinoma, with FHAD1, ZFPM2, DLG2, and HLA-DQA1 contributing to the association. Second, we conducted MR and found evidence for a positive association between TB infection and lung adenocarcinoma. Taken together, our findings further support an etiologic relationship between TB infection and lung cancer pathogenesis that may involve shared genetic factors.

According to the World Health Organization, an estimated 10.4 million people worldwide were afflicted with TB in 2016 [48], while 1.7 million people died from the disease. Over 95% of TB-related deaths occur in low and middle-income countries, with seven nations accounting for 64% of the total (i.e., China, India, Indonesia, Philippines, Pakistan, Nigeria,

and South Africa). In 2015, investigators from the Global Burden of Disease Study (GBD) estimated that 15% of the new TB cases (1.56 million) and 4% of TB-related deaths were reported in China [49], the region in which most of our participants resided. Evidence from multiple epidemiological and clinical studies support a link between pulmonary TB and lung cancer [6, 14, 17–21]. However, several studies did not detect an association [22–26], which could be due to the relatively low prevalence of TB in certain populations such as those in more affluent regions of Western countries [6]. As such, the relationship between TB and lung cancer has yet to be firmly established.

TB infection may influence lung cancer risk through biological mechanisms involving prolonged inflammatory/immunologic responses that lead to genetic alterations in proto-oncogenes and/or tumor suppressors [14–16, 50]. HLA-DQA1 was among the notable contributing genes in the pathway analysis and has a central role in regulating adaptive immune response. Previous studies found that variants of the HLA-DQA1 gene were associated with lung adenocarcinoma in a Japanese population [51], while several genomic investigations have found that various HLA variants in the MHC region were associated with lung cancer in Asian and European populations [8, 52].

The MFN2 gene encodes an outer membrane GTPase that contributes to regulating the morphology [53], fission, and fusion [54] of mitochondria, critical organelles that are primarily responsible for aerobic cellular respiration. The role of MFN2 in TB-susceptibility and lung cancer etiology is still unclear. However, a previous study found that MFN2 expression levels were nominally higher in peripheral blood mononuclear cells from TB-infected cases compared to controls [55]. Furthermore, MFN2 is a known hyperplasia suppressor gene [56] and a study of clinical tumor samples found that its expression was significantly higher in lung adenocarcinoma tissues compared to adjacent normal tissues [54]. When MFN2 was knocked down in A549 lung adenocarcinoma cell lines, cellular proliferation, cell cycle and invasion behavior were all deregulated [54]. Given that mitochondria regulates bioenergetics, metabolism, and apoptosis [57], which are key factors in both anti-microbial immunological/inflammatory response [58] and cancer development [59–61], it stands to reason that a regulator of mitochondrial function such as MFN2 may influence both diseases.

In summary, our study expanded upon existing data from the largest genomic study of never-smoking women in the world by identifying genetic factors related to TB susceptibility that may also influence lung adenocarcinoma development. Additionally, results from our MR analysis provide further support for a causal relationship between pulmonary TB and lung adenocarcinoma. Given the high prevalence of TB in low and middle-income countries in East Asia such as China, these findings may partially explain the high lung cancer rates in this susceptible population. Further observational and functional studies are required to replicate our findings and to unravel their biological significance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Top genetic variants located in tuberculosis-related genes that contributed to the association with lung adenocarcinoma among never-smoking Asian women

Gene	SNP, rs number	Chromosome	Position, GRCh37-hg19	Reference Allele	Effect Allele	Estimate, log OR	SE	P_{SNP}	P_{gene}
FHAD1	rs7539674	1	15597675	A	G	1.85	0.40	3.5E-06	0.001
HLA-DQA1	rs3129763	6	32590925	G	A	−0.58	0.18	1.2E-03	0.009
DLG2	rs 1311159	11	84695711	T	C	−0.15	0.04	1.3E-05	0.017
ZFPM2	rs2343595	8	106591207	G	C	0.09	0.03	5.9E-04	0.020
ZFPM2	-	8	106393057	T	C	−0.22	0.06	5.9E-04	0.020
ZFPM2	-	8	106546262	C	T	−0.16	0.05	8.7E-04	0.020
ZFPM2	rs35893068	8	106480315	T	C	−0.13	0.04	1.2E-03	0.020
ZFPM2	rs2343596	8	106593207	C	A	−0.09	0.03	2.1E-03	0.020
MEIS2	rs 12909569	15	37217527	A	G	−0.23	0.06	4.2E-04	0.067
MEIS2	rs3901057	15	37292836	G	A	0.13	0.04	0.002	0.067
MEIS2	rs17436991	15	37315283	T	C	−0.14	0.05	0.003	0.067
MEIS2	rs12708547	15	37227850	G	C	−0.10	0.03	0.004	0.067
MEIS2	rs4924117	15	37313594	C	T	0.09	0.03	0.005	0.067
LRRC69	rs7015316	8	92105675	C	T	1.68	0.61	0.006	0.068
LRRC69	rs78041518	8	92189901	A	G	−0.22	0.08	0.008	0.068
LRRC69	rs147312721	8	92170657	A	G	−0.41	0.16	0.009	0.068
LRRC69	-	8	92162739	G	A	−0.44	0.18	0.015	0.068
LRRC69	rs13256627	8	92123208	T	C	−1.57	0.67	0.019	0.068

Listed SNPs were selected by the sARTP method as the ones that contributed the most to the overall gene set-association in the pathway analysis. Each SNP was located in or within 20 kb upstream/downstream of each gene.