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Environmental Tobacco Smoke, Genetic Susceptibility, and Lung Cancer among Never Smokers

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Environmental Tobacco Smoke, Genetic Susceptibility, and Lung Cancer among Never Smokers

A dissertation submitted in partial satisfaction of the requirements

for the degree Doctor of Philosophy in Epidemiology

by

Claire Hahni Kim

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ABSTRACT OF THE DISSERTATION

Environmental Tobacco Smoke, Genetic Susceptibility,

and Lung Cancer among Never Smokers

by

Claire Hahni Kim

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2016

Professor Zuo-Feng Zhang, Co-chair

Professor Jian Yu Rao, Co-chair

Background

Although exposure to environmental tobacco smoke (ETS) is a well-established risk factor for lung cancer in never smokers, studies to date have not been able to precisely estimate the magnitudes of association between ETS and lung cancer by histological subtypes, especially for small cell lung cancer, large cell lung cancer, and adenocarcinoma in situ/minimally invasive carcinoma (AIS/MIA). In addition, few studies have investigated the roles of candidate susceptibility genes in lung cancer development and explored their potential interactions in relation to ETS exposure among never smokers.

Objectives and Specific Aims

The overall objective of this doctoral dissertation is to examine the associations of ETS exposure and variants of candidate genes with lung cancer susceptibility and to assess potential gene-environmental interactions among never smokers. The specific aims were: 1) To estimate the magnitudes of association between exposure to ETS and risk of lung cancer by major histological type (adenocarcinoma, squamous cell carcinoma, large cell lung cancer, and small cell lung cancer) and for AIS/MIA; 2) To estimate the associations between polymorphisms of DNA repair, carcinogen metabolism, and cell cycle control genes and lung cancer in never smokers and to test for gene-environmental interactions with ETS exposure; and 3) To evaluate the associations of genetic polymorphisms related to miRNAs and stem cell regulation with lung cancer susceptibility in never smokers and to assess potential gene-environmental interactions with ETS exposure.

Study Design and Population

We conducted case-control studies using pooled data from 18 studies participating in the International Lung Cancer Consortium (ILCCO) for Specific Aims 1 and 2 and pooled data from the Jiangsu Four Cancers Study and the Taiyuan Air Pollution and Lung Cancer Study for Specific Aim 3. The study populations in the ILCCO studies were racially diverse while all participants in the Jiangsu and Taiyuan Studies were Chinese. All studies provided epidemiologic data collected through interviews using structured questionnaires. There was a total of 12,667 cases (2,503 never smokers) and 14,410 controls (7,276 never smokers) in the pooled ILCCO data and 382 non-smoking cases and 1,271 non-smoking controls in the pooled data of Jiangsu and Taiyuan Studies.

Statistical Methods

We imputed the missing data for pack-years of smoking, education, and income using the median values among controls. Observations with missing data for other variables were excluded from the analyses. Potential confounders were adjusted for in data analyses, including age, sex, study or area of residence, race/ethnicity (ILCCO studies only), education (Chinese studies only), and income (Chinese studies only). We also adjusted for tobacco smoking status and pack-years of smoking in analyses including both ever and never smokers. We used multivariate unconditional logistic regression analyses to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI) for the associations and ratio of odds ratios (ROR) and 95% CI for gene-environmental interactions of interest. In order to mitigate sparse data bias, we employed the semi-Bayesian shrinkage method with informative priors based on the literature (when available) or a null-effect prior of OR=1.00 and 95% CI 0.25–4.00. Multiplicative interactions were assessed using the product-term method to estimate the ratio of odds ratios (ROR). Additive interactions were assessed by estimating the relative excess risk due to interaction (RERI).

Results

ETS and Lung Cancer among Never Smokers. In the pooled ILCCO data, the adjusted ORs of ETS exposure on lung cancer among never smokers was 1.31 (95% CI 1.17–1.47) for all histological types combined. When stratified by histological type, the adjusted ORs among never smokers were 1.26 (95% CI 1.10–1.45) for adenocarcinoma overall, 1.52 for (95% CI 1.03–2.24) AIS/MIA, 1.38 (95% CI 0.98–1.95) for squamous cell carcinoma, 1.50 (95% CI 0.90–2.48) for large cell lung cancer, 1.28 (95% CI 1.13–1.45) for non-small cell lung cancer overall, and 2.89

(95% CI: 1.53–5.45) for small cell lung cancer. After applying the semi-Bayes shrinkage approach with informative priors from the literature, the ORs were 1.24 (95% CI 1.16–1.31) for all histological types combined, 1.27 (95% CI 1.15–1.41) for adenocarcinoma overall, 1.47 (95% CI 1.02–2.14) for AIS/MIA, 1.38 (95% CI 1.05–1.82) for squamous cell carcinoma, 1.30 (95% CI 0.87–1.95) for large cell lung cancer, 1.23 (95% CI 1.15–1.30) for non-small cell lung cancer overall, and 1.97 (95% CI 1.30–3.00) for small cell lung cancer. The estimated magnitude of association with ETS exposure was greater for small cell lung cancer than for non-small cell lung cancer (ROR=2.08, 95% CI 1.10–3.94, P=0.024). In the combined analysis of the two Chinese studies, the pooled adjusted OR for ETS exposure on lung cancer risk was 1.46 (95% CI, 1.12–1.89).

Genetic Susceptibility Markers and Lung Cancer among Never Smokers. In the ILCCO pooled analysis, a positive association was observed between lung cancer susceptibility and the G allele in the DNA repair gene polymorphism *OGG1* S326C among those exposed to ETS (CG+GG vs. CC, Bayesian posterior OR=1.55, 95% CI 1.04–2.32). In addition, *ERCC2/XPD* D312N was also associated with an increased risk of lung cancer among those exposed to ETS (AA vs. GG, Bayesian posterior OR=1.48, 95% CI 1.01–2.16).

In the combined analysis of the Jiangsu Four Cancers Study and the Taiyuan Air Pollution and Lung Cancer Study, associations with lung cancer were observed for *CTTNB1* rs2953, *RAN* rs14035, *TP53INP1* rs7760, *TP53INP1* rs896849, *EPCAM* rs1126497, *HEY1* rs1046472, *HEY2* rs3734637, *OCT4* rs13409, and *WNT2* rs3729629.

Interactions between ETS and Genetic Susceptibility Factors. For the ILCCO pooled analysis, additive interactions were observed between *TP53* R72P and ETS on lung cancer. For the pooled Chinese case-control studies, there were statistical interactions between ETS exposure and *GEMIN4* rs7813 (multiplicative and additive), *WNT2B* rs2273368 (multiplicative and additive), *pre-miR-a46* rs2910164 (multiplicative), *AXIN* rs1981492 (multiplicative), and *WNT8A* rs4835761 (multiplicative).

Discussion and Conclusions

Our results confirm the role of ETS exposure in the development of lung cancer. Furthermore, the strengths of the associations vary by histological type and the association is stronger for small cell lung cancer than other histological types. This is the first large-scale collaborative study on the gene-environmental interactions between polymorphisms of DNA repair, carcinogen metabolism, cell cycle control, miRNA, and stem cell regulation genes and lung cancer susceptibility in never smokers. Our results add to the body of evidence demonstrating that polymorphisms of these genes affect lung cancer development in never smokers, and also suggest that some of these SNPs interact with ETS either multiplicatively or additively.

Public Health Implications

Identification of lung cancer susceptibility genes may aid in personalized risk prediction. A better understanding of the genetic, environmental, and behavioral risk factors for lung cancer in never smokers would help to identify those who need to be targeted for preventive interventions against lung cancer.

The dissertation of Claire Hahni Kim is approved.

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CONFERENCE PRESENTATIONS AND MEETING ABSTRACTS

1. **Kim CH**, Jin ZY, Zhou JY, *et al*. "Gene-environment interactions between polymorphisms of stem cell and microRNA-related genes and tobacco smoke exposure in lung cancer risk." Poster presentation delivered at the American Society of Preventive Oncology annual meeting, Columbus, OH, March 2016.
2. Zhou JY*, **Kim CH***, Han RQ, *et al*. "Interactions between lifestyle factors and active and passive exposure to tobacco smoke on the risk of lung cancer in a Chinese population." Oral presentation delivered at the American Public Health Association annual meeting, Chicago, IL, November 2015. *Co-first author
3. **Kim CH***, Zhou JY, Li L, *et al*. "Exposure to environmental tobacco smoke and lung cancer in Chinese populations: A meta-analysis of 30 studies." Oral presentation delivered at the American Public Health Association annual meeting, Chicago, IL, November 2015. *Co-first author

CHAPTER 1. INTRODUCTION AND BACKGROUND

1.1 Epidemiology of Lung Cancer

1.1.1 Global Burden of Lung Cancer

With an estimated 1.82 million new cases and 1.59 million deaths in 2012, lung cancer is the most commonly diagnosed cancer and the most common cause of death from cancer worldwide [5]. There have been major shifts in the global distribution of lung cancer over the past three decades, reflecting temporal changes in patterns of tobacco use [6]. In most developed countries, the decrease in smoking prevalence in men, from the late 1960s through the 1980s, has been driving lung cancer incidence and mortality rates downward [6]. The proportion of lung cancer patients in developing countries, on the other hand, has risen from 31% in 1980 to 58% of all lung cancers in the world in 2012, corresponding to the rapid rise in cigarette consumption in these countries [6].

1.1.2 Lung Cancer in the U.S.

In the U.S., lung cancer is the second most commonly diagnosed cancer type in both men and women, with an estimated 224,390 new cases in 2016 [7]. Lung cancer incidence in the U.S. is characterized by significant disparities by race, with black men having approximately 50% higher incidence than whites [8]. The incidence rates of lung cancer among men and women closely reflect the historical patterns of cigarette smoking over the past several decades, as the rates have been declining since the mid-1980s among men, and since the mid-2000s among women [7, 8]. However, lung cancer still accounts for more deaths than any other cancer in the

U.S. A total of 158,080 deaths are expected to occur due to lung cancer in 2016, of which approximately 80% will be attributable to cigarette smoking [7].

1.1.3 Lung Cancer in China

In China, lung cancer is the most frequently diagnosed cancer among men, the second most frequently diagnosed cancer in women, and the leading cause of cancer death in both men and women [9]. Approximately 653,000 new cases and 597,000 deaths of lung cancer occurred in China in 2012, accounting for 35.8% and 37.5% of all occurrences in the world, respectively [5]. The estimated numbers of new cases and lung cancer deaths in 2015 were 733,000 and 610,000, respectively [10]. Lung cancer mortality has risen 465% over the past three decades [11]. According to the Global Adult Tobacco Survey (GATS), approximately 301 million people smoke in China [12]. The prevalence of current tobacco smoking was 28.1% for all adults combined, 52.9% among men, and 2.4% among women in China during 2009-2010 [12]. In addition, 11.2% of male youth (ages 13-15) were reported as current tobacco users in the 2014 Global Youth Tobacco Survey [12]. Among nonsmokers, 72.4% were exposed to environmental tobacco smoke (ETS) and 38.0% were exposed on a daily basis [12].

1.1.4 Histological Types of Lung Cancer

Lung cancer is a heterogeneous disease commonly divided into two broad categories—small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). The major histological subtypes of NSCLC include squamous cell carcinoma, adenocarcinoma, and large cell lung cancer. Bronchioloalveolar carcinoma (BAC) is a subtype of adenocarcinoma with distinct molecular, pathologic, clinical, and epidemiologic features [13-17]. In 2011, the multidisciplinary team of

the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society recommended replacing the BAC classification with adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA), due to the wide spectrum of clinical and histologic characteristics within BAC [18]. Lung cancer arises from either the central airway compartment (mainly squamous cell carcinoma and small cell lung cancer) or from the peripheral airway compartment (mostly adenocarcinoma and large cell lung cancer), and previous studies have shown etiologic and prognostic heterogeneity by histological type, suggesting different underlying biological mechanisms and different responses to environmental assaults and clinical therapies [19-21].

1.1.5 Tobacco Smoking and Lung Cancer

The prevalence of smoking has been declining considerably in most high-income countries, but there has been little change, or even an increase, in many other countries [22]. Eastern and South-Eastern Asia and Eastern Europe are the regions with the highest smoking prevalence among males, whereas among females the prevalence is highest in European countries, followed by Oceania and Northern and Southern America [22]. The International Agency for Research on Cancer (IARC) has classified tobacco smoking as a Group 1 carcinogen and found 81 carcinogens in mainstream cigarette smoke to have sufficient evidence for carcinogenicity in humans or laboratory animals, including 11 carcinogens in Group 1, 14 in Group 2A, and 56 in Group 2B. [23]. Tobacco smoking is the most important risk factor for lung cancer, with estimated odds ratios (OR) of 23.9 (95% CI 19.7–29) for male current smokers, 7.5 (95% CI 6.2–9.1) for male former smokers, 8.7 (95% CI 7.4–10.3) for female current smokers, and 2.0 (95% CI 1.6–2.4) for female former smokers, compared with never smokers in European

countries [24, 25]. All histological types of lung cancer are associated with tobacco smoking, but the relationships are stronger for small cell lung cancer (OR=12.9, 95% CI 9.79–17.1) and squamous cell carcinoma (OR=11.3, 95% CI 9.39–13.5) than for large cell lung cancer (OR=5.64, 95% CI 4.15–7.67) and adenocarcinoma (OR=3.22, 95% CI 2.62–3.98) [26, 27]. Among adenocarcinomas, the estimated effect of tobacco smoking is weaker for AIS/MIA than for other subtypes [18, 28-32].

1.2 Lung Cancer in Never Smokers

1.2.1 Overview

Although most cases of lung cancer are attributable to tobacco smoking, approximately a quarter of all lung cancer cases worldwide occur among never smokers [33]. The definition of never smokers varies across studies, but the most commonly used definition is individuals who have smoked fewer than 100 cigarettes in their lifetime. The proportions of lung cancer in never smokers vary from 2-6% in men in Western countries to more than 50% in women in Southeast Asia [19, 34-36]. Adenocarcinoma is the most common histological type of lung cancer found in never smokers [34-36].

Risk factors for lung cancer in never smokers include family history, history of respiratory infection or disease, low consumption of fruit, low socioeconomic status, and exposures to ETS, domestic radon, occupational carcinogens (e.g., asbestos, polycyclic aromatic hydrocarbons), cooking and heating fumes, and indoor and outdoor air pollution [19, 23, 37-40]. Also, it has been suggested that hormonal factors in women may interact with other risk factors [39, 40].

1.2.2 Environmental Tobacco Smoke and Lung Cancer in Never Smokers

Environmental tobacco smoke (ETS) is a mixture of exhaled mainstream smoke and sidestream smoke released from the smoking device and diluted in ambient air. ETS is also referred to as secondhand tobacco smoke, and exposure to ETS is commonly called "secondhand smoking," "passive smoking," and "involuntary smoking." Passive smoking involves the inhalation of the same carcinogens inhaled during active smoking, although at much lower doses. Carcinogens contained in ETS include benzene, 1,3-butadiene, benzo[a]pyrene, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and many others [23]. The genotoxic activity of many components of ETS has been demonstrated [41-43]. Exposure to ETS leads to excretion of the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in the urine [44, 45]. Exposure to ETS also increases concentrations of DNA adducts of tobacco-related carcinogens [46, 47].

Active cigarette smoking is by far the most prevalent form of tobacco smoking and, therefore, it is the main source of exposure to ETS. A study on data from 192 countries reported that 33% of non-smoking men, 35% of non-smoking women and 40% of children worldwide were exposed to ETS in 2004 [48]. In a more recent study based on the Global Adult Tobacco Survey (GATS) data collected during 2009-2013, the estimated proportion of children exposed to ETS in the home was greater than 50% [49]. A large proportion of adults in low- and middle-income countries were also exposed to ETS in their homes (e.g., 73.1% in Vietnam), workplaces (e.g., 63.3% in China), and other public places (e,g., 79.6% on public transportation in Egypt and 88.5% in restaurants in China), according to data from GATS 2008-2010 [50]. In a study conducted in the U.S., tobacco metabolites were found in 90% of urine samples from children with parents

who smoke [51]. Women are more likely than men to be exposed to ETS at home, while the inverse is true for exposures at the workplace [23].

Based on the results of numerous studies, IARC estimated that exposure to ETS from the spouse increases the risk of lung cancer by 37% in men and 24% in women [23]. Studies have found linear trends for the association between risk of lung cancer and both the frequency and duration of exposure to ETS [52, 53]. In a review of 37 epidemiological studies, Hackshaw *et al*. reported never smokers who lived with a smoker were at a 26% increased risk of lung cancer compared with those who did not live with a smoker [52]. Dose-response relationships were observed between lung cancer risk and both the number of cigarettes smoked by the spouse and the duration of exposure. The pooled relative risk was higher for squamous and small cell carcinoma (RR=1.58, 95% CI 1.14–2.19) than for adenocarcinoma (RR=1.25, 95% CI 1.07–1.46) [52]. Similarly, a pooled analysis of two case-control studies reported that duration of exposure showed consistent dose-response relationships with adenocarcinoma and squamous and small cell carcinomas and suggested a higher risk for squamous and small cell carcinomas than for adenocarcinoma [54]. However, this previous analysis was limited by inadequate power for further analysis by each histological type of lung cancer. In most of the studies to date, the numbers of small cell and large cell lung cancer cases among never smokers have been too small to be studied in detail [55-57]. To the best of our knowledge, the study by Bracci *et al*. is the only published report on the association between ETS exposure and AIS/MIA [30]. In that study, ETS exposure in ever smokers and never smokers combined was not found to be associated with AIS (OR=0.95, 95% CI 0.57–1.6 and OR=1.1 95%, CI 0.60–2.1 among whites and nonwhites, respectively). However, the analysis included only 95 cases among never smokers.

1.2.3 Genetic Susceptibility to Lung Cancer in Never Smokers

Numerous studies have reported molecular differences between smokers and never smokers who develop lung cancer, indicating that lung cancer in never smokers is a distinct disease entity [35, 37, 58, 59]. Studies of genomic polymorphisms have found constitutive DNA variations across individuals according to their smoking status, particularly in genes associated with carcinogen metabolism, DNA damage repair, tobacco addiction, and inflammatory processes [38, 40]. Furthermore, tissue-based somatic mutations of the *TP53* and *KRAS* genes also vary with smoking status [60]. Epidermal growth factor receptor (EGFR) mutations and EML4-ALK fusions are more common in never smokers than in ever smokers [61-64]. The treatment response rates for EGFR tyrosine kinase inhibitors, such as gefitinib and erlotinib, are significantly higher in never smokers than in ever smokers with advanced non-small cell lung cancer, especially for adenocarcinoma [65-67]. Such findings support the idea that there are separate genetic and molecular paths to lung cancer for smokers and never smokers.

Recent genome-wide association studies (GWAS) have found common genetic variants at 5p15.33 (*TERT/CLPTM1L*), 6p21–6p22 (*BAT3/MSH5*) and 15q25.1 (*CHRNA5/CHRNA3/CHRNB4*) to be associated with lung cancer risk [68-74]. Truong *et al*. reported significant heterogeneity by smoking status and age of onset for SNPs at 15q25 [74]. In a pooled analysis of data from sixteen GWAS of lung cancer, Timofeeva *et al*. confirmed the previous findings for the associations between the loci at 5p15, 6p21-6p22, and 15q25, and identified a novel susceptibility locus at 9p21.3 specifically for squamous cell carcinoma [75]. In another GWAS involving four independent studies, Li *et al*. reported that rs2352028 at chromosome 13q31.3 was associated with lung cancer risk in never smokers through its

downregulation of GPC5 expression [76]. In a recent meta-analysis of GWAS of lung cancer in never-smoking Asian women, SNPs at 6p21.1, 9p21.3, and 12q13.13 achieved genome-wide significance [77]. Furthermore, some candidate gene studies and pathway-based analyses have identified susceptibility regions at 22q12 (*CHEK2*) [78, 79] and 15q15 (*TP53BP1*) [80-82]. Genetic regions at 3q28 [83], 13q12.12, and 22q12.2 [84] have been observed to be associated with lung cancer among Asian populations.

Epidemiologic studies have shown that individuals differ in their susceptibility to environmental exposures, suggesting there are gene-environment interactions in the development of lung cancer. Just as there have been found to be cancer susceptibility genes that act in conjunction with active smoking to modify the risk of lung cancer, there may be genes that interact with ETS to modify the risk of lung cancer in passive smokers.

1.2.4 Carcinogen Metabolism

Cells with DNA that have been damaged by carcinogens are usually destroyed in apoptosis, but some aberrant cells with acquired mutations escape normal cell cycle control and avoid apoptosis, which can lead to the development of lung cancer. Therefore, the ability to metabolize carcinogens is likely to play an important role in individual susceptibility to lung cancer. Phase I enzymes (such as cytochrome P450 enzymes) catalyze the addition of an oxygen atom to a carcinogen, thereby making it more water-soluble and readily excreted. Phase II enzymes (such as glutathione S-transferases) further increase this solubility and assist in detoxification [19]. However, some intermediate metabolites formed by Phase I enzymes bind to DNA at specific sites, resulting in bulky adducts. This can lead to apoptosis, removal of adducts by the DNA

repair system, or somatic mutations in *KRAS* or *TP53* genes [19]. Such genetic mutations can create genomic instability and other genetic and epigenetic changes leading up to the development of cancer. Some previous studies have observed that single nucleotide polymorphisms (SNPs) in exon 7 of cytochrome P450 1A1 (*CYP1A1*) and homozygous deletion of glutathione S-transferase (*GSTM1*) are associated with an increased risk of lung cancer in never smokers [43, 85-89]. Therefore, genetic polymorphisms of both Phase I and Phase II enzymes have been found to be associated with lung cancer risk in never smokers. Some studies have also observed that ETS modifies the association between polymorphisms of carcinogen metabolism genes and lung cancer [43, 85, 86], but others have found no effect [87]. Bennett *et al.* reported that, among female never smokers, homozygous carriers of the *GSTM1* null allele had greater risk of lung cancer from ETS than those who were heterozygous or homozygous carriers of the wildtype allele (OR=2.6, 95% CI 1.1–6.1) [43]. Kiyohara *et al.* reported similar findings, whereby individuals with *GSTM1* null genotype and high-dose ETS exposure (≥40 pack-years by husbands) had significantly higher risk of lung cancer compared with those with *GSTM1* non-null genotype and low-dose ETS exposure (<40 pack-years) (OR=2.27, 95% CI 1.13–4.57) [85].

1.2.5 DNA Damage Repair

DNA damage repair capacity might also affect susceptibility to lung cancer. Individuals with lower capacity to repair DNA may have a higher risk of lung cancer from DNA-damaging carcinogens, such as those contained in ETS. Gorlova *et al*. reported low levels of DNA repair capacity in never smokers were associated with increased risk of lung cancer (OR=1.92, 95% CI:1.3–2.9), especially in those exposed to ETS and those with a family history of lung cancer

[90]. Studies of polymorphisms of DNA repair genes have focused on those involved in base excision repair (e.g., *XRCC1, OGG1, APE1/APEX1*), nucleotide repair (*e.g., ERCC1, ERCC2*), double-strand break repair (e.g., *XRCC3*) and mis-match repair (e.g., *MLH1, MSH2*) [19]. Zhou *et al*. reported that the *XRCC1* Arg399Gln SNP was associated with an increased risk of lung cancer (OR=1.3, 95% CI 1.0–1.8) [91]. The polymorphism was associated with an increased risk of lung cancer among never smokers (OR=2.4, 95% CI 1.2–5.0), but a marginally decreased risk among heavy smokers (≥55 pack–years) (OR=0.5, 95% CI 0.3-1.0) [91]. However, their stratified analysis by smoking status was limited by low statistical power. Researchers have hypothesized that the effects of DNA repair polymorphisms might be overwhelmed in heavy smokers [91]. Significant associations have also been reported for polymorphism in other *XRCC* genes, including *XRCC3* (rs1799794) and *XRCC4* (rs1056503, rs9293337, and rs6869366) in a Chinese population [92] as well as *XRCC3* T241M in a pooled study of the International Lung Cancer Consortium (ILCCO) [93]. The NBS1 polymorphism rs1063054 was positively associated with lung cancer in a multi-center study by Park *et al*. [94]. In a study by Lee *et al.*, the CATA and CCCG haplotypes of the DNA repair gene *LIG1* were positively associated with lung cancer risk [95]. The *ERCC2* Asp312Asn polymorphism is associated with increased risk in ever smokers in some studies and in never smokers in others [96, 97]. Lo *et al*. reported that polymorphism of *MLH1* was associated with lung cancer in never smokers (OR=1.64, 95% CI 1.10–2.44), and that the association was modulated by ETS exposure [98]. Overall, studies on the association between DNA repair genes and lung cancer have identified only a few genetic polymorphisms consistently associated with lung cancer in never smokers, and the modifying effect of ETS also needs to be further studied.

1.2.6 Cell Cycle Control

Genes in the cell cycle control pathway are likely to be crucial in the development of lung cancer. Cells with damaged DNA must either pause in the cell cycle to be repaired or undergo apoptosis. Therefore, defects in the cell cycle pathway could result in carcinogenesis. The *TP53* tumor suppressor gene is a critical mediator of cellular response against genotoxic insults and has been the subject of many studies to date [99]. In a study by Husgafvel-Pursiainen *et al*., *TP53* mutations were more common in never smokers exposed to ETS than in those not exposed to ETS [100]. In the Taiyuan Air Pollution and Lung Cancer Study, two TP53 SNPs, rs2078486 and rs1042522, were positively associated with lung cancer among smokers and the total population, respectively, and multiplicative interaction was observed for rs2078486 with tobacco smoking and indoor air pollution [101]. Overall, studies on the relationship between polymorphisms of *TP53* and lung cancer risk have been inconsistent, and studies focusing on never smokers are scarce.

1.2.7 microRNA

Polymorphisms in microRNA (miRNA) sequences or binding sites of miRNAs may also contribute to lung cancer susceptibility. miRNAs, which are endogenous non-coding RNAs, are approximately 22 nucleotides long and typically function as negative regulators of post-transcriptional gene expression [102, 103]. They act through interaction of their seed region, mostly with the 3’ untranslated region (UTR) of the messenger RNA (mRNA) and with the 5’ UTR or protein coding regions [104]. miRNAs have great regulatory potential because a single miRNA molecule can target hundreds of mRNAs and the 3’ UTR of a single mRNA may have multiple binding sites for various miRNAs [104]. Furthermore, it has been reported that more

than 50% of genes are likely targets of specific regulation by miRNAs [105]. miRNAs play a crucial role in regulating various biological processes, including gene regulation, tumorigenesis, proliferation, apoptosis, and metabolism [106-109]. miRNA-related SNPs have the ability to inhibit the expression or activity of a tumor suppressor, or can enhance the expression or activity of an oncogene [110-113].

To date, only a few SNPs of miRNA sequences have been reported to be associated with lung cancer. In a case-control study in a Chinese population, the variant homozygote CC genotype of *miR-196a2* rs11614913 was associated with an increased risk of NSCLC compared with the TC/TT genotype (OR=1.25, 95% CI 1.01–1.54) [114]. In a case-control study in a Korean population, the TC/CC genotypes of *miR-196a2* rs11614913 were associated with an increased risk of NSCLC compared with the TT genotype among smokers (OR=1.42, 95% CI 1.03–1.96) but no association was observed among non-smokers (OR=1.29, 95% CI 0.66–2.52) [115].

1.2.8 Stem Cell Regulation

Although their role in carcinogenesis is not well characterized, increasing evidence suggests that stem cells could be the source of mutant cells that cause cancer. If, in fact, cancer stem cells are the driving force in cancer development, then traditional therapeutic methods that target the main tumor mass only, and not the cancer stem cells, will not be very effective [116]. Several signaling pathways, such as Wingless-type protein (Wnt), Hedgehog, and Notch, have been identified as key regulators of stem cells. Some of these pathways act as direct regulators while others act as indirect regulators.

The Wnt signaling pathway plays a crucial role in vertebrate development, cellular proliferation, differentiation, and carcinogenesis, including lung carcinogenesis [117]. Wnt is a glycoprotein that binds to Frizzled receptors and regulates the stabilization and localization of ß-catenin [118]. Once ß-catenin is stabilized through the Wnt signal, it is imported into the nucleus, and binds to transcriptional factors that regulate the expression of Wnt target genes [119]. In the absence of Wnt signaling, ß-catenin undergoes phosphorylation and degradation [120, 121].

Polymorphisms of genes encoding stem cell signaling molecules can contribute to carcinogenesis. For example, the axis inhibition protein (*AXIN*) acts as a tumor suppressor by limiting the deregulation of Wnt signaling that is commonly observed in a number of cancers [122, 123]. A meta-analysis of three studies reported the Pro50Ser polymorphism (rs2240308) of *AXIN2* was inversely associated with lung cancer risk in both smokers and non-smokers (dominant model, OR=0.64, 95% CI 0.41–0.99; OR=0.60, 95% CI 0.39–0.91, respectively) [124]. Recent studies have found that miRNAs regulate components of stem cell signaling pathways in ways that either promote or suppress progression of various cancers [125-128], including lung cancer [129, 130].

1.3 Gaps in the literature

There are several gaps in the epidemiologic literature regarding the relationship between ETS exposure and lung cancer in never smokers. Due to limitations in sample sizes, studies to date have not been able to precisely estimate the magnitudes of association between ETS exposure and specific histological types of lung cancer, especially for small cell lung cancer, large cell lung cancer, and AIS/MIA. Although many studies have examined the role of candidate

susceptibility genes in lung cancer, only a small proportion has focused on never smokers. Furthermore, most of the studies which did examine the molecular epidemiology of lung cancer in never smokers either lacked information on ETS exposure or had limited sample sizes and, therefore, were not able to test for interactions between ETS and genetic polymorphisms on lung cancer risk. Thus, the role of genetic susceptibility in the development of lung cancer among never smokers remains uncertain, and further studies are needed to better understand the complex roles of genetic factors and ETS exposure in lung carcinogenesis.

CHAPTER 2. RESEARCH OBJECTIVES AND METHODS

2.1 Research Objectives

The overall objective of this study is to examine the relationships between ETS exposure, genetic polymorphisms, and risk of lung cancer in never smokers. We will estimate the magnitude of association between ETS exposure and each major histological type of lung cancer as well as AIS/MIA. Furthermore, we will test for gene-environment interactions between ETS exposure and single nucleotide polymorphism of genes in the following pathways: carcinogen metabolism, DNA repair, cell cycle control, miRNA, and stem cell regulation.

2.2 Specific Aims and Hypotheses

Hypotheses for Specific Aim 1

1. Lung cancer is positively associated with ETS exposure overall, but there may be etiological heterogeneity in its relation to tobacco smoking across different histological types. We hypothesize that the magnitudes of associations are greater for squamous and small cell carcinomas of the lung (central region of the lung) than for adenocarcinoma and large cell lung cancer (outer area of the lung).
2. Since lung adenocarcinoma is associated with both active tobacco smoking and exposure to ETS, we hypothesize that the adenocarcinoma in situ/minimally invasive adenocarcinoma (AIS/MIA) subtype is also associated with lung cancer in never smokers.
3. As observed in active smoking and lung cancer, there is a dose-response relationship between duration of ETS exposure and lung cancer.

4. Exposure to ETS during childhood is associated with an elevated risk of lung cancer later in life.

Specific Aim 1

To estimate the magnitudes of association between ETS exposure and lung cancer susceptibility by major histological type (adenocarcinoma, squamous cell carcinoma, large cell lung cancer, and small cell lung cancer) and for AIS/MIA among never smokers within the ILCCO study population.

Hypotheses for Specific Aim 2

1. Polymorphisms of DNA repair genes are associated with lung cancer in never smokers.
2. Polymorphisms of carcinogen metabolism genes are associated with lung cancer in never smokers.
3. Polymorphisms of cell cycle control genes are associated with lung cancer in never smokers.
4. ETS exposure modulates the relationship between these genetic polymorphisms and lung cancer in never smokers.

Specific Aim 2

To examine the relationships between polymorphisms of DNA repair, carcinogen metabolism, and cell cycle control genes and lung cancer in never smokers and to test for potential gene-environment interactions with ETS exposure among never smokers within the ILCCO study population.

Hypotheses for Specific Aim 3

1. Polymorphisms of miRNA-related genes are associated with lung cancer in never smokers.
2. Polymorphisms of stem cell regulation genes are associated with lung cancer in never smokers.
3. ETS exposure modulates the relationship between these genetic polymorphisms and lung cancer in never smokers.

Specific Aim 3

To estimate the associations between genetic variants related to miRNAs and stem cell regulation and lung cancer susceptibility in never smokers and to test for potential gene-environment interactions with ETS exposure among never smokers in the combined study sample of two Chinese case-control studies.

2.3 Study Design and Methods

We conducted our analyses using pooled case-control data from the International Lung Cancer Consortium (ILCCO) for Specific Aims 1 and 2 and those from the Jiangsu Four Cancers Study and the Taiyuan Air Pollution and Lung Cancer Study for Specific Aim 3. All studies have been approved by UCLA IRB.

ILCCO

ILCCO was established in 2004 with the objective of sharing comparable data from ongoing lung cancer studies to increase the power for subgroup analysis. The consortium was established

with funding from the National Cancer Institute (NCI) and the IARC. Investigators with eligible epidemiologic studies of lung cancer were invited to participate in the ILCCO data pooling project. A total of 70 lung cancer studies have each provided a study protocol for subject recruitment and a structured questionnaire for lifestyle information in order to participate in ILCCO. Details of the studies in ILCCO included in the present analysis have been reported previously [87, 93, 131-146].

Jiangsu Study

The Jiangsu Four Cancers Study ("Jiangsu Study") is a large scale, community-based case-control study of the cancers of the lung, liver, stomach, and esophagus in a Chinese population. Jiangsu Province, located in South-Eastern China, is an ideal location for conducting such a study due to its well-established cancer registry and high incidence of cancer. Study participants were recruited from four counties in Jiangsu Province—Chuzhou, Dafeng, Ganyu and Tongshan—covering a population of approximately 4.3 million. All participants provided informed consent prior to entering the study. Details of this study have been described previously [147].

Taiyuan Study

The Taiyuan Study of Air Pollution and Lung Cancer ("Taiyuan study") is a population-based case-control study conducted in Taiyuan, the capital city of Shanxi province in China. The aim of the study was to investigate the role of indoor air pollution in the development of lung cancer by exploring indoor activity, living habits, and housing characteristics in relation to risk of lung cancer, with a focus on Chinese non-smoking women. Details of this study have been reported

previously [101, 148].

2.4 Study Population

Specific Aim 1

For Specific Aim 1, data from 18 case-control studies in ILCCO were pooled (Table 2-1). Eight studies were conducted in North America; four studies were conducted in Europe; and six studies were conducted in Asia/Oceania. Eight studies recruited healthy controls from the general population; eight studies recruited controls from hospital patients or their family or friends who did not have any smoking-related illnesses; and two studies recruited controls from mixed sources. Fifteen studies matched cases with controls on potential confounders, such as age, sex, and ethnicity, while three studies did not use matching. Written informed consents were obtained from all study participants, and each study was approved by its respective local human subject review board.

The most commonly used definition of never smokers was those who smoked less than 100 cigarettes in their lifetime (the FHS, UCLA, WELD, NELCS, SLRI, Harvard, Mayo, and IARC studies). Other definitions included those who smoked less than 180 cigarettes in their lifetime (the Hawaii study), those who smoked less than 200 cigarettes in their lifetime (the Seoul study), those who smoked less than 365 cigarettes in their lifetime (the Kyushu, Moffitt, and GEL-S studies), those who never smoked more than ten cigarettes per week regularly (the Liverpool study), or those who either smoked less than 400 cigarettes in their lifetime or less than one cigarette per day for one year (the CREST study). The Aichi and GenAir studies defined never smokers as those who reported they had never smoked.

The data for Specific Aim 1 included 12,667 lung cancer cases and 14,410 controls, of whom 2,503 cases and 7,262 controls were never smokers and 10,164 cases and 7,148 controls were current or former smokers. Cases included patients with invasive tumors of the lung using either the International Classification of Diseases for Oncology (ICD-O) version 2 or the International Classification of Diseases (ICD), Ninth or Tenth Edition.

For the analysis on AIS/MIA, we pooled all seven studies with data on ETS exposure and at least five cases of AIS/MIA among never smokers within the ILCCO study population. These cancers were classified as BAC in the original studies because the studies were conducted prior to year 2011, when the new histological classification system was recommended. The pooled data consisted of 627 cases of AIS/MIA, of whom 171 were never smokers, and 7,642 controls, of whom 3,165 were never smokers.

Specific Aim 2

For Specific Aim 2, we invited study investigators in ILCCO to participate in an analysis of ETS exposure and SNPs of the DNA repair, carcinogen metabolism, and cell cycle regulation pathways among never smokers. A total of seven studies agreed to share their data for the present analysis. The pooled data included information on demographic characteristics, history of active smoking and exposure to ETS, genotypes for the SNPs of interest, and lung cancer histology among the cases. We excluded 4 subjects whose age was unknown. The final pooled data for the present analysis consisted of 745 cases and 2,606 controls, all of whom were classified as never smokers.

Specific Aim 3

In the Jiangsu Study, eligible cases were patients with a pathologically or clinically confirmed diagnosis of primary cancer of the lung, liver, stomach, or esophagus reported to the population-based cancer registry of one of the four counties between January 1, 2003 and December 31, 2010. All cancer cases were classified according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) and the International Classification of Diseases for Oncology, 2nd edition (ICD-O-2). Cases were identified through a rapid reporting system in which all regional hospitals were required by the local health authorities to report new cancer patients within a month after diagnosis. As the cancer registry departments are housed within the local CDC, investigators from the local CDC were able to identify and interview cases promptly after their diagnosis. Cases were required to be at least 18 years old, residents of the respective county for at least five years, and in stable medical condition as determined by their physician. Second primary and recurrent cancer cases were excluded.

Potential controls for the Jiangsu Study were identified through the demographic database of each county. For each cancer case, a control was randomly selected from a list of residents living in the same county and within the same sex and age group (±5 years). Controls were required to be at least 18 years old, had lived in the respective county for at least five years, without any history of cancer, and in stable medical condition (i.e., apparently healthy individuals, not otherwise submitted to any screening). When individuals did not meet the eligibility criteria or refused to participate in the study, their basic demographic data were recorded and the same

selection process was used to identify another potential control. Based on estimated power calculations for examining various exposure-cancer associations and gene-environment interactions, the original plan was to conduct a 1:1 matched study with 600 cases and 600 healthy controls for each cancer site in each county, for a total of 2,400 cases and 2,400 controls for each cancer site. However, we subsequently decided to pool together all controls in order to increase the statistical power of the study.

The participation rate among lung cancer patients in the Jiangsu Study was 63% and that of controls was 87%. A total of 2,781 lung cancer patients served as cases for the Jiangsu Study, of whom 1,799 provided their blood samples. In addition, 6,650 out of a total of 8,019 controls provided their blood samples. At the time of the present analysis, genotyping data were available for cases and controls from Dafeng and Ganyu Counties only. After excluding smokers, a total of 205 non-smoking cases and 989 non-smoking controls with both questionnaire data and genotyping data were included in the present analyses.

In the Taiyuan Study, eligible cases were lung cancer patients diagnosed for the first time between 2005 and 2007 at Shanxi Tumor Hospital. Cases had to be at least 20 years old, have lived in Taiyuan for at least 10 years, and be in stable medical condition. Controls were randomly selected from the thirteen communities covering the largest areas in Taiyuan. Controls were matched to cases by age, sex, and area of residence. Controls also had to be at least 20 years of age, have lived in Taiyuan for at least 10 years, and with no history of cancer or any other serious chronic disease. All participants provided written informed consent. The response rates were 89% and 85% among cases and controls, respectively. Overall, there were 399 cases

and 466 controls, of whom 177 cases and 282 controls were never smokers with both questionnaire and genotyping data.

2.5 Data Collection

ILCCO

Each study in ILCCO used a structured questionnaire to collect epidemiologic data, including exposure ETS at home and the workplace. There were some variations in the wording of the questions regarding exposure to ETS. For example, the Mayo Clinic study asked, "Were/are you regularly exposed to environmental (second-hand) cigarette smoke (from father, mother, or spouse)?" whereas the Harvard study asked, "How often does someone smoke inside your home?" Other information included ETS exposure duration, intensity, and childhood exposure history. We checked the pooled data for inadmissible values, aberrant distributions, inconsistencies, and missing values and sent queries to the participating investigators to resolve all issues.

The SNPs were selected by each participating study based on a candidate gene approach, whereby the genotypes of variants implicated to play a role in lung carcinogenesis were obtained. For the current pooled analysis, we included all candidate SNPs for which data were available from at least two studies. The genetic variants analyzed in Specific Aim 2 using data from ILCCO are listed below in Table A.

Table A. DNA repair, cell cycle, and carcinogen metabolism SNPs from ILCCO studies included in Specific Aim 2

Pathway	Gene	SNP
DNA repair		
Base excision repair	*APEX* D148E	rs3136820
	OGG1 S326C	rs1052133
	XRCC1 R194W	rs1799782
	XRCC1 R399Q	rs25487
Double strand break repair	*XRCC2* R188H	rs3218536
	XRCC3 T241M	rs861539
Nucleotide excision repair	*ERCC1* T354C	rs11615
	ERCC1 C8092A	rs3212986
	ERCC2/XPD D312N	rs1799793
	ERCC2/XPD K751Q	rs13181
	ERCC5/XPG H1104D	rs17655
Cell cycle		
	TP53 R72P	rs1042522
Carcinogen metabolism	*CYP1A1* T3801C	rs4646903
	CYP1A1 I462V	rs1048943
	GSTM1	Deletion
	GSTT1	Deletion
	GSTP1 I105V	rs947894
	ATM C77T	rs664677

Jiangsu Study and Taiyuan Study

The same structured questionnaire was used in both the Jiangsu Study and the Taiyuan Study. Trained interviewers conducted in-person interviews which took an average of 45 minutes, during which measurements of the participant's height, weight, and blood pressure were also taken. In the Jiangsu Study, cases were interviewed either in the hospitals or their homes, while controls were interviewed in their homes. In the Taiyuan Study, cases were interviewed at the hospital and controls were interviewed in community health services centers. The interviews of cases took place as soon as new cancers were reported and registered in the cancer registry system. Data regarding the stage and histological type of cancer were not collected by the cancer

registries and, therefore, are not available for analysis. If a case was too ill to be interviewed, a family member served as a proxy respondent.

Based on the recent findings reported in the literature suggesting potential effects of miRNA and stem cell related genetic polymorphism on cancer risk, we selected for our analyses 28 miRNA-related SNPs and 25 stem cell SNPs listed in Table B below.

Table B. MicroRNA and stem cell SNPs in Jiangsu and Taiyuan Studies included in Specific Aim 3

MicroRNA		Stem cell	
Gene	**SNP**	**Gene**	**SNP**
Ago2	rs4961280	*AXIN1*	rs1981492
CDK6	rs42031	*AXIN2*	rs2240308
CTNNB1	rs2953	*Ctbp2*	rs3740535
CXCL12	rs1804429	*Dec1*	rs2269700
Dicer1	rs3742330	*DLL1*	rs1033583
DOCK4	rs3801790	*DLL1*	rs1421
Drosha	rs10719	*DVL2*	rs222851
E2F2	rs2075993	*EpCAM*	rs1126497
Gemin3	rs197412	*FZD1*	rs3750145
Gemin4	rs2740348	*FZD3*	rs2241802
Gemin4	rs7813	*GLI1*	rs2228224
IL15	rs10519613	*HES2*	rs11364
IL6R	rs4072391	*HES2*	rs8708
KRAS	rs9266	*HEY1*	rs1046472
miR-196a2	rs11614913	*HEY2*	rs3734637
miR-26a1	rs7372209	*JAG2*	rs9972231
miR-27	rs895819	*Notch1*	rs3815188
PPARGC1A	rs3774923	*Notch4*	rs915894
pre-miR-146a	rs2910164	*Notch4*	rs520692
Ran	rs14035	*Oct4*	rs13409
Rbl2	rs3929	*Oct4*	rs3130932
RCHY1	rs2126852	*Rex1*	rs6815391
TAB3	rs3816757	*WNT2*	rs4730775
THBS1	rs2292305	*WNT2*	rs3729629
TP53INP1	rs896849	*WNT8A*	rs4835761
TP53INP1	rs7760		
Wnt2B	rs2273368		
WWOX	rs12828		
XPO5	rs11077		

2.6 Laboratory Analysis

ILCCO

ILCCO studies used the following genotyping platforms: UCLA and Kyushu used RFLP, Harvard, Seoul, and GEL-S used TaqMan, IARC used both TaqMan and Amplifluor, and GenAir used both TaqMan and PE/DHPLC.

Jiangsu Study

Approximately 5-8 mL of non-fasting peripheral blood samples were collected successfully from 63% of lung cancer cases and 83% of controls. Blood specimens were collected into both EDTA- and whole blood tubes and assigned an identification number. They were then separated into serum, red blood cells, and white blood cells and stored below -20°C at the local CDCs, after which they were transported to the Jiangsu CDC, and stored below -70°C. The biological specimens were then transferred to the Molecular Epidemiology Laboratory at UCLA and DNA was extracted. Finally, genotyping was performed at the UCLA Genotype and Sequencing Core using a customized Fluidigm Dynamic 96.96 Array™ Assay (Fluidigm, South San Francisco, CA).

Taiyuan Study

In the Taiyuan Study, blood samples were collected from 98% of cases and 99% of controls, using both EDTA and whole blood tubes. They were then separated into serum, red blood cells, and white blood cells and stored below -20°C at the Taiyuan CDC, after which they were transported to Fudan University School of Public Health, and stored below -70°C freezers. The biological specimens were then transferred to the Molecular Epidemiology Laboratory at UCLA. A modified phenolcholoform protocol was used to extract genomic DNA. Finally, genotyping was performed at the UCLA Genotype and Sequencing Core using a customized Fluidigm Dynamic 96.96 Array™ Assay (Fluidigm, South San Francisco, CA).

2.7 Statistical Analysis

For our overall analyses of both smokers and non-smokers using ILCCO data, we excluded participants with unknown smoking status (n=63), age (n=31), or race/ethnicity (n=251). We also excluded 10,442 participants with unknown ETS exposure status, of whom 7,541 were from the IARC, Moffit, or GenAir study. The IARC and Moffitt studies collected information regarding ETS exposure from never smokers only, and the GenAir study collected information regarding ETS exposure from those who either never smoked or who had stopped smoking for at least ten years. The cases and controls excluded due to unknown ETS exposure status had similar distributions of age, sex, and race/ethnicity as those included in the analysis. For ever smokers whose data for pack-years of smoking was missing, we imputed the median value of the controls stratified by sex and age group (<50, 50-59, 60-69, 70-79, and 80 years old or above). For analyses with only non-smoking cases and controls, we excluded all current or former smokers and participants with unknown age (n=4).

Because the same questionnaire was used in both the Jiangsu Study and the Taiyuan Study, the data pooling process did not require harmonizing across the two Chinese studies. After merging the data from the two studies, we created a subset for never smokers only. Never smokers were defined as individuals who had smoked no more than 100 cigarettes in their lifetime. Individuals who had either lived with someone who smoked in the household or worked with someone who smoked in the workplace were classified as “exposed to ETS”. We compared the distributions of basic socio-demographic factors among cases and controls using the Chi-squared test. For the analyses of the Chinese studies, we imputed missing data for education and income levels using

the median values of the controls stratified by sex, area of residence (Dafeng, Ganyu, or Taiyuan), and age group.

We performed unconditional logistic regression to obtain odds ratios (OR) with 95% confidence intervals (CI) to assess the associations of ETS exposure and lung cancer risk. All models were adjusted for age (continuous) and sex. Models using ILCCO data in Specific Aim 1 were further adjusted for race/ethnicity (White/Caucasian, Latino, Black/African-American, Asian, or other) and study was treated as a random-effect variable to account for heterogeneity across study populations. The SAS procedure GLIMMIX was used to obtain profile penalized likelihood CIs. Models using Chinese studies data in Specific Aim 3 were further adjusted for area of residence (Dafeng, Ganyu, or Taiyuan), educational level (no formal education, primary school, or middle school and above) and income level 10 years ago (<1,000; 1,000-1,999; 2,000-2,999; or 3,000 Yuans/year and above). .

We also assessed various aspects of ETS exposure, including location, duration, and childhood exposure. Exposure duration variables included duration of exposure at home, duration of exposure at the workplace, and duration of exposure at home and work combined. The combined duration of exposure variable was created by summing the values for duration of exposure at home and duration of exposure at work—thus, it is the maximum possible duration of exposure, since there could be overlap between exposure periods. For the Chinese studies, we also examined intensity of ETS exposure (none, slight, medium, or heavy). We conducted two-tailed trend tests for the duration and intensity of exposures by assigning scores to ordinal levels of

exposure and testing the significance of the regression parameter of the variable treated as a continuous variable in the logistic regression model.

For Specific Aim 1, we performed separate analyses by lung cancer histology to compare the estimated associations of ETS with different histological subtypes among the overall and non-smoking populations. When comparing small cell lung cancer with non-small cell lung cancers, we employed a case-case approach [132, 133, 149, 150]. Furthermore, we examined the joint associations of active smoking and ETS exposure and tested for multiplicative interaction in the ILCCO study populations using a logistic regression model with a product term.

For the ILCCO studies, we performed the analyses among the total sample and among never smokers separately. When analyzing the data among the total sample, we further adjusted the models for cigarette smoking status (ever smoker or never smoker) and pack-years of cigarette smoking (continuous) in order to separate the qualitative difference between ever smokers and never smokers from the quantitative impact of smoking. The sub-analysis of never smokers allowed us to completely eliminate the confounding effect of active smoking, assuming there was no misclassification of ever/never smoking status.

We tested for heterogeneity across the study odds ratios by using the likelihood ratio test, in which we examined the difference between the log likelihood of a model with the product term between study and the variable of interest, and that of a model without such a product term. When there was evidence of heterogeneity in the study-specific odds ratios, we assessed the source of heterogeneity by stratified analyses. If the heterogeneity was not due to any study

characteristic, we examined forest plots and performed influence analysis to assess the source of heterogeneity from any single study. For influence analysis, each study was excluded one at a time to assure that the magnitude of the overall summary estimate and P-value were not dependent on any one study.

Since the sample sizes for some of the subgroup analyses were rather small, in order to mitigate sparse-data bias, we used the data augmentation approach of the semi-Bayes shrinkage method [151, 152]. For the priors, we searched the literature for estimates of association to be used as informative priors and used a null prior of OR=1.00 (95% CI 0.25–4.00) for all SNPs. Table C summarizes the prior information used in our analyses. We carried out stratified analyses by age (<65 years old vs. ≥65 years old) and sex. Stratification by race among the ILCCO study population was not possible due to the limited sample sizes of non-whites. All statistical analyses were performed using SAS 9.4 and two-sided P-values are reported (α=0.05).

Table C. Priors used in semi-Bayesian shrinkage analyses

Variable	Prior OR (95% CI)	Source
Informative Priors		
ETS exposure (ever vs. never)	1.21 (1.13-1.30)	US Surgeon General Report (2006)[a]
Adenocarcinoma	1.28 (1.13-1.44)	Boffetta (2002)[b]
Squamous cell carcinoma	1.38 (0.87-2.20)	Boffetta (2002)
Non-small cell lung cancer	1.21 (1.13-1.30)	None found (Used the estimate for lung cancer overall.)
Small cell lung cancer	1.47 (0.84-2.56)	Boffetta (2002)
ETS exposure at home	1.21 (1.13-1.30)	US Surgeon General Report (2006)
ETS exposure at workplace	1.22 (1.13-1.33)	US Surgeon General Report (2006)
ETS exposure in childhood	1.11 (0.94-1.31)	US Surgeon General Report (2006)
Non-informative (Null) Prior		
Large cell lung cancer	1.00 (0.50-2.00)	
ETS exposure for AIS/MIA	1.00 (0.50-2.00)	
SNP	1.00 (0.25-4.00)	

[a]Reference #153
[b]Reference #154

Analysis of Genetic Polymorphisms

We tested whether each SNP in the ILCCO studies was in Hardy-Weinberg equilibrium among the controls in each study using the Chi-square test with P<0.01. The *OGG1* S326C SNP in the Harvard study was not in Hardy-Weinberg equilibrium among the controls. Therefore, we excluded the Harvard study from the analysis of *OGG1* S326C.

All SNPs from the Chinese studies included in the present analysis had a genotyping call rate greater than 90%, a minor allele frequency greater than 5%, were in Hardy-Weinberg equilibrium among the controls using a Bonferonni adjusted P-value cutoff of 5×10^{-4} (≈0.05/96), and were not in linkage disequilibrium.

We used unconditional logistic regression models to estimate genotype-specific ORs and 95% CIs. We compared heterozygous and homozygous carriers of the minor allele with the homozygous carriers of the major allele. We also examined the OR per variant allele and P-values for trend assuming a log-additive genetic model with 1 degree of freedom. All models were adjusted for age (continuous), sex, and ETS exposure status (ever/never); models for ILCCO studies were further adjusted for study; and models for Chinese studies were further adjusted for educational level (no formal education, primary school, or middle school and above), income level 10 years ago (<1,000; 1,000-1,999; 2,000-2,999; or 3,000 Yuans/year and above), and area of residence (Dafeng, Ganyu, or Taiyuan). Because there were some cells with sparse data, we applied the semi-Bayes shrinkage method using data augmentation, with a null prior of OR=1 and variance of 0.5 (equivalent to 95% CI 0.25–4.00) for the associations between each SNP and lung cancer [151, 152]. We also performed stratified analyses by ETS exposure status and examined the joint associations of each SNP with ETS exposure in a dominant model of genetic effect. We evaluated multiplicative interaction using the product-term method and additive interaction by estimating the relative excess risk due to interaction (RERI) [155].

For the analysis of Specific Aim 3 based on Chinese studies data, we constructed a polygenic risk score (PRS) variable as a parsimonious way of summarizing the effects of genetic variants for each subject [156]. The PRS was constructed as the weighted sum of all SNPs which were associated with lung cancer with a P-value less than 0.1 in the dominant genetic model. The weight of each SNP was determined by the adjusted log OR of its association with lung cancer. We then categorized the PRS variable into quartiles based on its distribution among the controls.

CHAPTER 3. RESULTS

3.1 ETS Exposure and Lung Cancer by Histological Type (Specific Aim 1)

The distributions of basic characteristics of the lung cancer patients and controls among the overall population and among the subsample of never smokers are shown in Table 3-1. The contribution of cases from the individual studies ranged from 1% to 33% and that of controls ranged from 1% to 16%. The majority of the cases and controls lived in North America. In both the overall population and the never smoker population, the proportion of older participants (65 years or above) was higher among the cases than among the controls. The proportion of men was higher in cases than in controls among the overall population, but lower among the never smoker population. The proportion of adenocarcinoma was higher among never smokers than among the overall population; the proportions of squamous cell carcinoma and small cell carcinoma were lower among never smokers than among the overall population; the proportions of large cell lung cancer were similar between the two populations.

The distributions of demographic characteristics and tobacco exposure status of AIS/MIA cases and controls are presented in Table 3-2. The cases were more likely than the controls to be 60 years old or above, female, white non-Hispanic, ever smokers, and ever exposed to ETS. The adjusted OR for the estimated effect of tobacco smoking was 1.97 (95% CI 1.62–2.39; results not shown).

Table 3-3 shows the joint associations and multiplicative interactions between active and passive smoking. Exposure to ETS was associated with an increased risk of lung cancer among both ever

smokers and never smokers, and multiplicative interactions were observed between active smoking and exposure to ETS for all histological types combined (ratio of odds ratios [ROR]=1.33, 95% CI 1.15–1.53), adenocarcinoma (ROR=1.44, 95% CI 1.21–1.72), and non-small cell lung cancer (ROR=1.36, 95% CI 1.16–1.59).

Table 3-4 reports the associations between exposure to ETS and lung cancer by histological subtype in the overall study population and among never smokers. The estimates of association were generally similar between the overall population and among never smokers, with the exception of the estimate for small cell lung cancer. Also, the estimates obtained from the ILCCO data were in close agreement with the informative prior estimates we found from the literature. Compared with those never exposed to ETS, those ever exposed were at a higher risk of lung cancer (OR=1.34, 95% CI 1.24–1.45 in the total population; OR=1.31, 95% CI 1.17–1.47 among never smokers). Positive associations were observed for all of the histological types examined, with the strongest association observed for small cell lung cancer (among never smokers, OR=1.26, 95% CI 1.10–1.45 for adenocarcinoma; OR=1.38, 95% CI 0.98–1.95 for squamous cell carcinoma; OR=1.50, 95% CI 0.90–2.48 for large cell lung cancer; OR=2.89, 95% CI 1.53–5.45 for small cell lung cancer; and OR=1.52, 95% CI 1.03–2.24 for AIS/MIA).

Table 3-5 compares small cell lung cancer with non-small cell lung cancer in terms of their association with ETS exposure. The adjusted ORs comparing small cell lung cancer with non-small cell lung cancer were 1.27 (95% CI 1.02–1.57, P=0.032) and 2.08 (95% CI 1.10–3.94, P=0.024) in the overall population and among never smokers, respectively.

Table 3-6 shows the associations between location of ETS exposure and lung cancer by histological type. Overall, estimates of association did not differ significantly by exposure location, but the strongest associations were observed for individuals who were exposed both at home and the workplace—the adjusted odds ratios among never smokers were 1.21 (95% CI 1.05–1.39) for those exposed at home, 1.10 (95% CI 0.95–1.29) for those exposed at work, and 1.29 (95% CI 1.12–1.50) for those exposed both at home and at the workplace.

Estimates of associations between duration of ETS exposure at home and lung cancer by histological type are presented in Table 3-7. Lung cancer susceptibility tended to increase with increasing years of ETS exposure at home in the total sample, but a dose-response relationship was not observed among never smokers. Table 3-8 shows the duration of ETS exposure at the workplace and lung cancer by histological type. We did not observe clear patterns of dose-response relationships for duration of ETS exposure at the workplace. Associations between ETS exposure at the workplace and lung cancer were observed in the highest category (>20 years) only. ORs for the combined duration of ETS exposure mostly exhibited weak positive trends (Table 3-9).

No apparent association was observed between lung cancer and childhood exposure to ETS (Table 3-10, never smokers OR=1.09, 95% CI 0.93–1.27).

Exposure to ETS was associated with AIS/MIA with adjusted ORs of 1.54 (95% CI 1.18–2.00) in the total sample and 1.52 (95% CI 1.03–2.24) in never smokers (Table 3-4). ETS exposure location, duration, and childhood exposure were inconsistently associated with AIS/MIA.

3.2 Polymorphisms of DNA Repair, Carcinogen Metabolism, and Cell Cycle Control Genes and Lung Cancer in Never Smokers (Specific Aim 2)

The distributions of major characteristics of the cases and controls in Specific Aim 2 are shown in Table 3-11. The IARC study contributed the largest number of samples (167 cases and 717 controls), followed by the Harvard study (149 cases and 454 controls). Age was distributed similarly between cases and controls, with cases being slightly older than controls (Mean age of 61 and 58 among cases and controls, respectively). The majority of both cases and controls were female (79% and 57%, respectively) and non-Hispanic white was the largest racial group (53% and 78% of cases and controls, respectively), followed by Asian (42% and 18% of cases and controls, respectively). The most prevalent histological type of lung cancer among cases was adenocarcinoma (60%).

Table 3-12 presents the adjusted ORs for the associations between genetic variants and lung cancer in all never smokers and stratified by ETS exposure status. There was a positive trend in lung cancer susceptibility with increasing number of G alleles in *OGG1* S326C (rs1052133), especially among those exposed to ETS (CG vs. CC OR=1.53, 95% CI 0.98–2.38; GG vs. CC OR=2.24, 95% CI 0.97–5.15; P_{trend}=0.015). The homozygous variant genotype of *ERCC2/XPD* D312N (rs1799793) was associated with an increased risk of lung cancer among those exposed to ETS (AA vs. GG OR=1.59, 95% CI 1.05–2.40; Bayesian posterior OR=1.48, 95% CI 1.01–2.16). We did not observe any significant main effects by SNPs in the carcinogen metabolism or cell cycle control pathways.

Joint associations and interactions between genetic variants of DNA repair, carcinogen metabolism, and cell cycle control pathways and ETS exposure are presented in Table 3-13. We did not observe any gene-environment interactions on the multiplicative scale but observed additive interaction for *TP53* R72P (RERI=0.50, 95% CI 0.09–0.91).

3.3 Polymorphims of miRNA and Stem Cell Related Genes and Lung Cancer in Never Smokers (Specific Aim 3)

Table 3-14 shows the distributions of demographic characteristics of cases and controls in the Jiangsu and Taiyuan Studies. Overall, cases were more likely than controls to be female and less educated. In both studies, female never smokers were more prevalent than male never smokers, as one would expect based on the known smoking rates among men and women in China. The subjects in the Jiangsu Study tended to be older than those in the Taiyuan Study (mean age of 61 and 53 years, respectively). The distributions of educational levels differed considerably between the two studies. Participants in the Taiyuan Study were generally more educated than those in the Jiangsu Study, in which approximately half of the participants had received no formal education.

Table 3-15 shows the estimates of associations between ETS exposure and lung cancer by study. Compared with those who were not exposed to ETS, those who were exposed were significantly more likely to develop lung cancer in both studies (Jiangsu, OR=1.46, 95% CI 1.05–2.02; Taiyuan, OR=1.65, 95% CI 1.04–2.63). Most cases and controls who reported ETS exposure were exposed at home only. In the Taiyuan Study, there was a marked increase in lung cancer risk among those who were exposed to ETS at work—a finding which has been reported previously [148]. A clear positive trend between exposure duration and lung cancer was

observed in the Jiangsu Study (P=0.003) but not in the Taiyuan Study (P=0.146). In addition, there was a dose-response relationship between intensity of ETS exposure and lung cancer in the Jiangsu Study (light vs. none, OR=1.10, 95% CI 0.68–1.78; medium vs. none, OR=1.43, 95% CI 0.92–2.22; heavy vs. none, OR=1.97, 95% CI 1.24–3.12; P_{trend}=0.003).

Adjusted odds ratios for the associations between miRNA-related SNPs and lung cancer are shown in Table 3-16. Positive associations with lung cancer were observed for the GG genotype of *CTNNB1* rs2953 (Bayesian posterior OR=1.64, 95% CI 1.06–2.54), the C allele of *GEMIN4* rs7813 among those unexposed to ETS (CT vs. TT, Bayesian posterior OR=1.77, 95% CI 1.18–2.67; CC vs. TT, Bayesian posterior OR=1.68, 95% 0.99–2.85), and the TT genotype of *miR-26a1* rs7372209 among those exposed to ETS (Bayesian posterior OR=1.64, 95% CI 1.00–2.69). The heterozygous genotypes of *miR-300* rs12894467, *pre-miR-146a* rs2910164, *EPCAM* rs1126497, *HEY1* rs1046472, and *HEY2* rs3774637 in never smokers overall, and *AXIN1* rs1981492 among those unexposed to ETS, were associated with lung cancer.

Table 3-17 shows the joint associations and interactions between miRNA and stem cell regulation SNPs and ETS exposure on lung cancer in never smokers. Interactions were observed on both the multiplicative scale and the additive scales for both *GEMIN4* rs7813 (Bayesian posterior ROR=0.50, 95% CI 0.31–0.73; RERI= -1.18, 95% CI -2.29 – -0.07) and *WNT2B* rs2273368 (Baysian posterior ROR=1.72, 95% CI 1.02–2.90; RERI=0.60, 95% CI 0.17–1.02). There were also multiplicative interactions between ETS exposure and *pre-miR-a46* rs2910164 (Bayesian posterior ROR=0.51, 95% CI 0.30–0.87), *AXIN* rs1981492 (Baysian posterior

ROR=0.56, 95% CI 0.34–0.91), and *WNT8A* rs4835761 (Bayesian posterior ROR=0.56, 95% CI 0.33–0.95).

There were a total of 8 SNPs which were associated with lung cancer with a P-value of less than 0.1 in the dominant genetic model—*RAN* rs14035, *TP53INP1* rs7760, *TP53INP1* rs896849, *EPCAM* rs1126497, *HEY1* rs1046472, *HEY2* rs3734637, *OCT4* rs13409, and *WNT2* rs3729629. ORs for the polygenic risk score involving those top 8 SNPS most strongly associated with lung cancer are presented in Table 3-18. The OR comparing the highest level of PRS with the lowest level of PRS was 2.52 (95% CI 1.69–3.75). The results did not differ significantly when stratified by ETS exposure status.

CHAPTER 4. DISCUSSION

4.1 ETS Exposure and Lung Cancer by Histological Type

The present analysis is the largest collaborative effort investigating the association between exposure to ETS and risk of lung cancer by histological type. Exposure to ETS was associated with an increased risk of lung cancer among both ever smokers and never smokers. In the overall pooled data of 18 ILCCO studies, exposure to ETS increased the risk of lung cancer by approximately 30% and 60% for non-small cell lung cancer and small cell lung cancer, respectively. Among never smokers, ETS exposure increased the risk by approximately 30% and 200% for non-small cell lung cancer and small cell lung cancer, respectively. In addition, our results also provide weak evidence that exposure to ETS increases the risk of AIS/MIA in never smokers.

Results of our joint association analyses suggest that exposure to ETS is associated with lung cancer in both ever smokers as well as never smokers. The strong association between ETS exposure and lung cancer in ever smokers might be related to the fact that smokers exposed to ETS tend to smoke more than unexposed smokers do, as was the case in the present analysis—the mean pack-years of smoking was 42.3 among those exposed to ETS, compared with 34.5 among those who were unexposed (t-test $P<0.0001$; results not shown). However, the association remained strong even after adjusting for pack-years of smoking (OR=1.40, 95% CI 1.25–1.56; results not shown). Therefore, a potential alternative explanation for this finding is that mainstream smoke and sidestream smoke have a synergistic effect on lung cancer development,

as also suggested by a recent report of significant interactions between active and passive smoking in Hong Kong [157].

Our results also indicate that the association with ETS exposure may be greater for small cell lung cancer than for the other histological types (P=0.024). This observation is consistent with the point estimates reported in previous studies by Hackshaw *et al.* and Brennan *et al.* which also evaluated the association between ETS and lung cancer risk, but with small and squamous cell carcinomas combined [52, 54]. Detecting such clear associations has been particularly challenging for small cell lung cancer due to the small number of cases among never smokers. In our study, the difference in the magnitudes of the association among the overall population compared with never smokers may be due to chance or residual confounding.

Epidemiologic studies have consistently reported that cigarette smoking is most strongly associated with small cell lung cancer, followed by squamous cell carcinoma [26, 40, 55, 150, 158-162]. The differences in the strengths of associations by histological type are thought to be related to tumor location. Small cell lung cancer and squamous cell carcinoma mainly occur in the large central bronchi whereas adenocarcinoma and large cell lung cancer arise from more peripheral sites. The aerodynamic diameters of cigarette smoke particles determine the sites of deposition in the regions of the lung [162]. It has been hypothesized that sites that are more proximal in the respiratory tract are more heavily exposed to tobacco smoke particles, especially those of larger size, than are peripheral sites [163-165]. De Stefani *et al*. suggested that the presence of carcinogenic radioactive compounds and heavy metals in tobacco smoke could also explain the strong relation between exposure to tobacco smoke and small cell lung cancer, since

occupational exposure to these carcinogens are strongly associated with small cell lung cancer [150]. Many of these carcinogens (e.g., nickel, chromium, and arsenic) are also major constituents of sidestream smoke [23]. The results of our study suggest that cigarette smoke plays a major role in the development of small cell lung cancer not only in the form of mainstream smoke affecting active smokers but also in the form of sidestream smoke affecting both active and passive smokers.

Lung cancer histology seems to be dictated by genetic alterations and the type of cells in which they occur. In a study using precise laser capture microdissection and allelotyping, Wistuba *et al*. reported there were differences in specific genetic alterations detected in small cell lung cancer compared with non-small cell lung cancers, and the smoking-damaged bronchial epithelium of patients with small cell lung cancer showed considerably more genetic damage—in terms of allele loss and microsatellite alterations—than that of patients with non-small cell lung cancers [166]. Furthermore, many genetic alterations were also frequently observed in histologically normal and mildly abnormal bronchial biopsies from current and former smokers [166]. Rb and p53 mutations, which occur in up to 90% of human small cell lung cancers, are examples of genetic damage caused by smoking. In a study to establish a mouse model for small cell lung cancer, Meuwissen *et al*. demonstrated that concomitant loss of Rb and p53 in a broad range of mouse lung epithelial cells gave rise almost exclusively to small cell lung cancer [167]. Although the cellular origin of lung cancer is largely unknown, it is speculated that different histological types arise from distinct cells of origin located in defined microenvironments, and small cell lung cancer is thought to have its origin in neuroendocrine cells [167, 168].

We also observed some variations in strengths of associations by the location and duration of ETS exposure. Exposure at home seemed to have a stronger effect than exposure at the workplace, probably because exposure at home—especially from a spouse—is more likely to be of greater duration and intensity than exposure at work. The results also suggest that people exposed to ETS both at home and at the workplace are more likely to develop lung cancer than those exposed at one location only. For both exposure at home and exposure at work, we observed weak dose-response relations between duration of exposure and lung cancer incidence. The trends were more evident among the overall population than among the subgroup of never smokers, possibly due to the difference in sample sizes. Brennan *et al.* also reported such dose-response relations among never smokers, but their method of categorizing duration of exposure differed from ours [54]. When we used the same duration categories used by Brennan *et al.* (<16/16-30.9/≥31.0 years for exposure from the spouse—assumed to be comparable to our variable for exposure at home—and <8.0/8.0-20.9/≥21.0 years for exposure at work), we observed dose-response relations among never smokers for both exposure at home (P=0.04) and exposure at work (P=0.02). Lastly, exposure to ETS during childhood was not significantly associated with lung cancer in the ILCCO data. Results from previous studies of exposure to ETS during childhood have been inconsistent, which could be, at least partially, due to the difficulty of recalling exposures that took place a long time ago [169-182]. The inconsistency may also be due to chance, since some of those studies had low power.

4.2 Genetic Polymorphisms and Lung Cancer in Never Smokers

The results of our pooled analysis using data from ILCCO suggest that lung cancer in never smokers may be positively associated with the variant genotypes of *OGG1* S326C (rs1052133)

and *ERCC2*/*XPD* D312N (rs1799793) among individuals exposed to ETS. In a previous analysis of ILCCO data among ever smokers and never smokers combined, Hung *et al*. had also observed a positive association between *OGG1* S326C and lung cancer among non-Hispanic whites (GG vs. CC OR=1.34, 95% CI 1.01–1.79) but not among Asians (OR not reported) [93]. However, in a case-control study in Taiwan, *OGG1* S326C was associated with an increased risk of lung cancer in heavy smokers (GG vs. CC OR=3.52, 95% CI 1.54–8.06) but not among moderate smokers (GG vs. CC OR=1.45, 95% CI 0.74–2.83) and never smokers (GG vs. CC OR=1.11, 95% CI 0.74–1.65), with a P value for interaction of 0.01 [183]. In a meta-analysis of 17 case-control studies, the genetic variant of *ERCC2/XPD* D312N was associated with an increased risk of lung cancer (AA vs. GG OR=1.24, 95% CI 1.09–1.42) [184]. However, when stratified by smoking status, the association was significant among smokers (CC vs. AA OR=1.48, 95% CI 1.23–1.79) but not among nonsmokers (CC vs. AA OR=1.38, 95% CI 0.78–2.19) [184]. To the best of our knowledge, previous reports on *OGG1* S326C and *ERCC2/XPD* D312N have not presented results for never smokers stratified by ETS exposure status. It is plausible that the lower DNA repair capability induced by polymorphisms of *OGG1* and *ERCC2/XPD* increases the risk of lung cancer among individuals with oxidative DNA damage caused by carcinogens tobacco smoke.

In the pooled analysis of the Jiangsu and Taiyuan Studies, we estimated that ETS exposure increased the risk of lung cancer in never smokers by approximately 50-60%, and both duration and intensity of exposure were positively associated with lung cancer development in a dose-response manner. Our results suggest that lung cancer development in never smokers may be influenced by polymorphisms of *CTTNB1* rs2953, *RAN* rs14035, *TP53INP1* rs7760, *TP53INP1*

rs896849, *EPCAM* rs1126497, *HEY1* rs1046472, *HEY2* rs3734637, *OCT4* rs13409, and *WNT2* rs3729629. Furthermore, there were statistical interactions between ETS exposure and *GEMIN4* rs7813, *WNT2B* rs2273368, *pre-miR-a46* rs2910164, *AXIN* rs1981492, and *WNT8A* rs4835761.

There have been several recent studies reporting associations between *pre-miR-146a* rs2910164 and lung cancer. A meta-analysis by Nikolić *et al*. reported that the C allele of *pre-miR-146a* rs2910164 was associated with an increased risk of lung cancer (GC vs. GG OR=1.04, 95% CI 0.92–1.18; CC vs. GG OR=1.20, 95% CI 1.03–1.40) [185]. In a Chinese population of female never smokers, Yin *et al*. observed that the G allele of *pre-miR-146a* rs2910164 was inversely associated with risk of lung cancer (CG vs. CC OR=0.76, 95% CI 0.59–0.99; GG vs. CC OR=0.64, 95% CI 0.46–0.90) [186]. Similarly, Jeon *et al*. also reported inverse associations between the G allele of *pre-miR-146a* rs2910164 and lung cancer risk in Korean never smokers (OR=0.66, 95% CI 0.45–0.96) [187]. We, on the other hand, observed null associations in our overall data (CG vs. CC OR=1.14, 95% CI 0.86–1.51; GG vs. CC OR=1.19, 95% CI 0.83–1.72).

To our knowledge, the present study is the first to report on the associations of *CTNNB1* rs2953 and *RAN* rs14035 with lung cancer. In a study of lung cancer cell lines and surgical specimens of lung cancer, Sunaga *et al*. reported that constitutive activation of the Wnt signaling pathway caused by mutations in exon 3 of *CTNNB1* may be involved in the development and progression of adenocarcinoma [188]. The mRNA expression of Ran protein in lung squamous cell carcinoma tissues have been observed to be significantly higher than in the adjacent normal tissues [189].

4.3 Strengths and Limitations

This study has several limitations. Due to the nature of our case-control study design, the results might have been influenced by recall bias. Since tobacco is an established risk factor for many diseases, hospital-based controls might be more likely than healthy controls to recall their exposure to ETS. If this is in fact the case among the ILCCO studies, our results from hospital-based case-control studies might be more likely to be biased towards the null, compared to those from population-based studies. However, when we performed stratified analysis, the association between exposure to ETS and lung cancer was even stronger within the stratum of hospital-based studies than that of population-based studies. Variations in the definition of never smokers across studies in ILCCO could also be a limitation. However, consistent results from influence analysis confirmed that the observed associations were not due to any particular study.

Another potential source of bias might be the result of misclassification of ever smokers as never smokers due to misreporting. In addition, the concordance of smoking status within couples might lead to bias of the estimates. However, a European validation study has suggested that such bias from smoker misclassification is not likely to be significant [190]. The prevalence of smoking reported by participants in the Jiangsu and Taiyuan Studies was consistent with the known rates in China.

We excluded some participants from the analysis due to missing data, mostly on exposure status. Selection bias is possible if the data were not missing at random. However, comparing those excluded from the analysis with those included, the distributions of the covariates were similar between the two groups, except for study site. There may have been uncontrolled residual

confounding by other risk factors such as occupational exposures, indoor air pollution, and diet but we do not suspect these other putative risk factors would have been strongly associated with our exposures of interest.

The data used in our analyses, especially those from ILCCO, did not come from a homogeneous population, but rather from distinct studies, with differences in population characteristics (e.g., race/ethnicity and lifestyle factors), questionnaire wording, and various other aspects of study design and protocol. Therefore, we tried to minimize the effects of such differences across studies by either adjusting for the study variable or treating the study variable as a random-effect variable in our regression models. The pooled Chinese studies data for Specific Aim 3, on the other hand, were based on an ethnically homogeneous population, identical questionnaires, and very similar study designs and protocols.

We did not have sufficient statistical power to obtain stable estimates for some of the SNPs, especially when stratifying on ETS exposure and testing for gene-environment interactions. We tried to mitigate potential sparse data bias by applying semi-Bayesian shrinkage to our estimates. Nevertheless, we still cannot rule out the possibility that at least some of our positives findings are false positives, especially considering that we performed a large number of tests using the same data (i.e., multiple comparisons). Therefore, future studies are warranted to validate our findings from this study.

Despite the limitations discussed above, this is one of very few molecular epidemiologic studies of lung cancer susceptibility focusing on never smokers and effect modification by ETS

exposure. The strength of this study is the relatively high power achieved through the pooling of individual-level data. Compared with meta-analyses, pooled analyses such as ours can achieve high power with less publication bias and more consistent covariate adjustment. Furthermore, we were able to investigate SNPs which had not been investigated in previous studies in relation to lung cancer in never smokers.

CHAPTER 5. CONCLUSION AND PUBLIC HEALTH IMPLICATIONS

In this study with the largest sample size of ILCCO, we confirmed the role of ETS exposure in the development of lung cancer regardless of histological type. Furthermore, we discovered that the ETS-lung cancer associations vary by histological type and is especially strong for small cell lung cancer. This is the first large-scale collaborative study on the association between polymorphisms of DNA repair, carcinogen metabolism, cell cycle control, miRNA, and stem cell genes and lung cancer in never smokers in relation to ETS exposure. Our results add to the body of evidence that polymorphisms of genes involved in these pathways affect lung cancer development in never smokers, and also suggest that some of these SNPs interact with ETS either multiplicatively or additively on the susceptibility of lung cancer.

In the U.S., when the causal relationship between tobacco smoking and lung cancer became known, the government and society campaigned to control and ban smoking in public places, thereby reducing lung cancer incidence. In contrast, preventive efforts in China have not been sufficient to decrease lung cancer incidence, especially among younger smokers and individuals with lower levels of education [191]. Although China ratified the World Health Organization Framework Convention on Tobacco Control in 2005 and signed the Protocol to Eliminate Illicit Trade and Tobacco Products in 2013, legislation against smoking in public places has not been strictly enforced, and the availability of cheap brands of tobacco products discourages smokers from attempting to quit [191].

It is important to continue to conduct research into the etiology of lung cancer among never smokers, as the worldwide prevalence of cigarette smoking steadily decreases and the proportion of lung cancer among never smokers rises. Identification of lung cancer susceptibility genes may aid in personalized risk prediction and individualized therapy. Recent epidemiologic studies report that risks of lung cancer are especially high among non-smoking Asian women due to the combined effects of ETS exposure, indoor and outdoor air pollution, various lifestyle factors, and genetic susceptibility. A better understanding of the genetic, environmental, and behavioral risk factors for lung cancer in never smokers would help to identify those who need to be targeted for preventive interventions against lung cancer.

Future studies on lung cancer in never smokers should determine if varying levels of intensity and duration of exposure to ETS is associated with stage of lung cancer, as well as consider potential interactions with other risk factors, such as exposure to indoor and outdoor air pollution. Studies should also examine the effects of SNPs on specific histological subtypes of lung cancer and whether there exist gene-gene interactions.

Table 2-1. Summary of ILCCO studies pooled

Project/institute by region	Study name	Principal investigator	Control source	Study period	Study location
North America					
Family Health Study	FHS	A.G. Schwartz	Population	1984-1987, 1990-2003	Detroit, MI, USA
University of California at Los Angeles	UCLA	Z.F. Zhang	Population	1999-2004	Los Angeles, CA, USA
Women's Epidemiology of Lung Disease	WELD	A.G. Schwartz	Population	2001-2005	Detroit, MI, USA
New England Lung Cancer Study	NELCS	E. Duell	Population	2005-2008	New Hampshire & Vermont, USA
Samuel Lunenfeld Research Institute	SLRI	J. McLaughlin	Mixed	1997-2002	Toronto, Canada
Harvard University	Harvard	D. Christiani	Hospital	1992-2008	Boston, MA, USA
Mayo Clinic	Mayo	P. Yang	Hospital	1997-2006	USA
Moffitt	Moffitt	P. Lazarus	Hospital	1999-2003	Florida, USA
Europe					
European Prospective Investigation into Cancer and Nutrition	GenAir	P. Vineis	Population	1993-1998	10 European countries
Cancer of the Respiratory Tract Biorepository	CREST	M. Neri	Mixed	1996-present	Northern Italy
Liverpool Lung Project	Liverpool	J. Field	Population	1998-2016	Liverpool, UK
International Agency for Research on Cancer	IARC	P. Boffetta	Hospital	1998-2002	Central/Eastern Europe
Asia and Oceania					
University of Hawaii	Hawaii	L. Le Marchand	Population	1992-1997	Hawaii, USA
Kyushu University	Kyushu	C. Kiyohara	Population	1994-1996	Japan
Genes and Environment in Lung Cancer, Singapore	GEL-S 1	A. Seow	Hospital	1996-1998	Singapore
Genes and Environment in Lung Cancer, Singapore	GEL-S 2	A. Seow	Hospital	2005-2007	Singapore
Aichi Cancer Center	Aichi	K. Tajima/ K. Mastuo	Hospital	2001-2005	Aichi, Japan
Seoul University	Seoul	Y.C. Hong	Hospital	2001-2008	Seoul, Korea

Table 3-1. Distribution of characteristics of lung cancer cases and controls in ILCCO studies

	All			Never Smokers		
	Cases, n (%)	**Controls, n (%)**	***P*[a]**	**Cases, n (%)**	**Controls, n (%)**	***P*[a]**
Total	12,667	14,410		2,503	7,262	
Study			<0.001			<0.001
FHS	970 (7.7)	1,154 (8.0)		376 (15.0)	664 (9.1)	
UCLA	609 (4.8)	1,038 (7.2)		109 (4.3)	470 (6.5)	
WELD	571 (4.5)	567 (3.9)		52 (2.1)	279 (3.8)	
NELCS	276 (2.2)	251 (1.7)		11 (0.4)	95 (1.3)	
SLRI	439 (3.5)	921 (6.4)		152 (6.1)	455 (6.3)	
Harvard	2,107 (16.6)	1,510 (10.5)		135 (5.4)	479 (6.6)	
Mayo	4,192 (33.1)	2,235 (15.5)		635 (25.4)	812 (11.2)	
Moffitt	117 (0.9)	380 (2.6)		39 (1.6)	303 (4.2)	
GenAir	74 (0.6)	702 (4.9)		47 (1.9)	466 (6.4)	
CREST	401 (3.2)	551 (3.8)		45 (1.8)	237 (3.3)	
Liverpool	286 (2.3)	888 (6.2)		17 (0.7)	247 (3.4)	
IARC	255 (2.0)	1,012 (7.0)		198 (7.9)	831 (11.4)	
Hawaii	628 (5.0)	587 (4.1)		45 (1.8)	224 (3.1)	
Kyushu	190 (1.5)	108 (0.8)		59 (2.4)	57 (0.8)	
GEL-S 1	261 (2.1)	673 (4.7)		149 (5.9)	585 (8.1)	
GEL-S 2	367 (2.9)	748 (5.2)		228 (9.1)	642 (8.4)	
Aichi	453 (3.6)	815 (5.7)		117 (4.7)	319 (4.4)	
Seoul	471 (3.7)	270 (1.9)		89 (3.6)	97 (1.3)	
Region			<0.001			<0.001
North America	9,909 (78.2)	8,643 (60.1)		1,554 (62.1)	3,781 (52.1)	
Europe	1,016 (8.0)	3,151 (21.9)		307 (11.2)	1,781 (24.5)	
Asia/Oceania	1,742 (13.7)	2,614 (18.1)		642 (25.6)	1,700 (23.4)	
Age (years)						
< 50	1,910 (15.1)	3,322 (23.0)	<0.001	493 (19.7)	1,814 (25.0)	<0.001
50-59	2,703 (21.3)	3,602 (25.0)		555 (22.2)	1,837 (25.3)	
60-69	3,940 (31.1)	3,980 (27.6)		693 (27.7)	1,903 (26.2)	
70-79	3,437 (27.1)	2,900 (20.1)		581 (23.2)	1,366 (18.8)	
≥ 80	677 (5.3)	606 (4.2)		181 (7.2)	342 (4.7)	
Mean (SD)	*62.9 (11.7)*	*59.3 (13.2)*		*61.5 (13.0)*	*58.7 (13.5)*	
Sex			<0.001			<0.001
Male	6,366 (50.3)	6,562 (45.5)		596 (23.8)	2,294 (31.6)	
Female	6,301 (49.7)	7,848 (54.5)		1,907 (76.2)	4,968 (68.4)	
Race/Ethnicity			<0.001			0.019
Non-Hispanic White	9,461 (74.7)	10,137 (70.3)		1,542 (61.6)	4,688 (64.6)	
Asian	2,291 (18.1)	3,211 (22.3)		774 (30.9)	2,023 (27.9)	
Black/African-American	536 (4.2)	617 (4.3)		100 (4.0)	324 (4.5)	
Hispanic/Latino	114 (0.9)	261 (1.8)		44 (1.8)	132 (1.8)	
Other	265 (2.1)	184 (1.3)		43 (1.7)	95 (1.3)	
Histology			<0.001			<0.001
Adenocarcinoma	5,997 (47.3)			1,555 (62.1)		
Squamous cell carcinoma	2,595 (20.5)			211 (8.4)		
Large cell lung cancer	650 (5.1)			95 (3.8)		
Unspecified non-small cell	789 (6.2)			91 (3.6)		
Small cell lung cancer	1,175 (9.3)			79 (3.2)		
Other/mixed/unknown	1,461 (11.5)			462 (18.9)		

[a]P-values are for χ^2-tests comparing cases and controls.

Table 3-2. Distribution of characteristics of lung AIS/MIA cases and controls in ILCCO studies

	All			Never smokers		
	Cases, n (%)	**Controls, n (%)**	***P*[a]**	**Cases, n (%)**	**Controls, n (%)**	***P*[a]**
Total	627	7,642		171	3,165	
Study			<0.001			0.002
Mayo	247 (39.5)	2,235 (30.2)		67 (39.2)	812 (25.7)	
Harvard	196 (31.3)	1,510 (19.8)		28 (16.4)	479 (15.1)	
FHS	34 (5.4)	1,084 (14.3)		25 (14.6)	615 (19.7)	
UCLA	39 (6.2)	1,038 (13.6)		18 (10.5)	470 (14.8)	
WELD	59 (9.4)	567 (7.4)		16 (9.4)	279 (8.8)	
Hawaii	38 (6.1)	587 (7.7)		12 (7.0)	224 (7.1)	
CREST	14 (2.2)	551 (7.2)		5 (2.9)	237 (7.5)	
Age (years)			<0.001			<0.001
< 50	67 (10.7)	2,182 (28.5)		29 (17.0)	1,048 (33.1)	
50-59	117 (18.7)	1,835 (24.0)		28 (16.4)	713 (22.5)	
60-69	213 (34.0)	1,844 (24.1)		49 (28.6)	647 (20.4)	
70-79	194 (30.9)	1,372 (17.9)		51 (29.8)	544 (17.2)	
≥ 80	36 (5.7)	409 (5.4)		14 (8.2)	213 (6.7)	
Mean (SD)	*64.4 (11.1)*	*58.1 (14.1)*		*63.3 (13.6)*	*57.1 (15.1)*	
Sex			<0.001			<0.001
Male	215 (34.3)	3,680 (48.2)		37 (21.6)	1,150 (36.3)	
Female	412 (65.7)	3,962 (51.8)		134 (78.4)	2,015 (63.7)	
Race/ethnicity			<0.001			0.002
Non-Hispanic White	541 (86.3)	6,276 (82.1)		132 (77.2)	2,504 (79.1)	
Asian	35 (5.6)	477 (6.2)		18 (10.5)	236 (7.5)	
Black/African-American	25 (4.0)	582 (7.6)		7 (4.1)	292 (9.2)	
Hispanic/Latino	10 (1.6)	227 (3.0)		8 (4.7)	102 (3.2)	
Other	16 (2.5)	80 (1.1)		6 (3.5)	31 (1.0)	

AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; ETS, environmental tobacco smoke

[a]P-value for χ^2-tests comparing cases and controls.

Table 3-3. Joint associations and multiplicative interactions of active smoking and exposure to ETS on lung cancer by histological type

Active smoking	Exposed to ETS	Cases, N	Controls, N	OR (95% CI)[a]
All Histological Types				
Never	Never	651	2,167	1.00 (Reference)
Never	Ever	1,816	4,879	1.18 (1.06-1.30)
Ever	Never	1,219	1,073	2.65 (2.34-3.01)
Ever	Ever	8,824	5,912	4.45 (4.04-4.90)
Multiplicative interaction ROR[a]				*1.33 (1.15-1.53)*
Adenocarcinoma				
Never	Never	422	2,167	1.00 (Reference)
Never	Ever	1,119	4,879	1.19 (1.05-1.35)
Ever	Never	482	1,073	1.89 (1.61-2.21)
Ever	Ever	3,919	5,912	3.26 (2.90-3.67)
Multiplicative interaction ROR[a]				*1.44 (1.21-1.72)*
Squamous Cell Carcinoma				
Never	Never	52	2,167	1.00 (Reference)
Never	Ever	156	4,879	1.21 (0.91-1.62)
Ever	Never	373	1,073	6.58 (4.98-8.70)
Ever	Ever	1,994	5,912	11.02 (8.56-14.20)
Multiplicative interaction ROR[a]				*1.10 (0.77-1.57)*
Large Cell Lung Cancer				
Never	Never	22	2,167	1.00 (Reference)
Never	Ever	72	4,879	1.15 (0.75-1.75)
Ever	Never	53	1,073	4.46 (2.80-7.09)
Ever	Ever	492	5,912	7.04 (4.83-10.25)
Multiplicative interaction ROR[a]				*1.13 (0.64-2.00)*
Non-Small Cell Lung Cancer				
Never	Never	520	2,167	1.00 (Reference)
Never	Ever	1,411	4,879	1.19 (1.06-1.33)
Ever	Never	958	1,073	2.65 (2.31-3.04)
Ever	Ever	7,049	5,912	4.47 (4.02-4.97)
Multiplicative interaction ROR[a]				*1.36 (1.16-1.59)*
Small Cell Lung Cancer				
Never	Never	13	2,167	1.00 (Reference)
Never	Ever	65	4,879	1.14 (0.74-1.75)
Ever	Never	135	1,073	7.01 (4.66-10.57)
Ever	Ever	943	5,912	13.22 (9.15-19.10)
Multiplicative interaction ROR[a]				*0.78 (0.41-1.48)*

ETS, environmental tobacco smoke; aOR, adjusted odds ratio; CI, confidence interval; ROR, ratio of odds ratios
Study is treated as a random-effect variable.
[a]Odds ratios are adjusted for age, sex, and race/ethnicity.

Table 3-4. Associations between exposure to ETS and lung cancer by histological type

	All				Never Smokers			
Exposed to ETS	**Ca, N**	**Co, N**	**OR (95% CI)[a]**	**Bayesian Posterior OR (95% PL)**	**Ca, N**	**Co, N**	**OR (95% CI)[b]**	**Bayesian Posterior OR (95% PL)**
All Histological Types								
Never	1,870	3,240	1.00 (Reference)	1.00 (Reference)	651	2,167	1.00 (Reference)	1.00 (Reference)
Ever	10,640	10,791	1.34 (1.24-1.45)	1.27 (1.20-1.33)	1,816	4,879	1.31 (1.17-1.47)	1.24 (1.16-1.31)
P for heterogeneity[c]			*0.009*				*0.005*	
Adenocarcinoma								
Never	904	3,240	1.00 (Reference)	1.00 (Reference)	422	2,167	1.00 (Reference)	1.00 (Reference)
Ever	5,038	10,791	1.35 (1.23-1.48)	1.32 (1.23-1.42)	1,119	4,879	1.26 (1.10-1.45)	1.27 (1.15-1.41)
P for heterogeneity[c]			*0.253*				*0.032*	
Squamous Cell Carcinoma								
Never	425	3,240	1.00 (Reference)	1.00 (Reference)	52	2,167	1.00 (Reference)	1.00 (Reference)
Ever	2,150	10,791	1.35 (1.16-1.57)	1.35 (1.17-1.56)	156	4,879	1.38 (0.98-1.95)	1.38 (1.05-1.82)
P for heterogeneity[c]			*0.064*				*0.351*	
Large Cell Lung Cancer								
Never	75	3,240	1.00 (Reference)	1.00 (Reference)	22	2,167	1.00 (Reference)	1.00 (Reference)
Ever	564	10,791	1.37 (1.04-1.80)	1.31 (1.02-1.69)	72	4,879	1.50 (0.90-2.48)	1.30 (0.87-1.95)
P for heterogeneity[c]			*0.665*				*0.207*	
Non-Small Cell Lung Cancer								
Never	1,478	3,240	1.00 (Reference)	1.00 (Reference)	520	2,167	1.00 (Reference)	1.00 (Reference)
Ever	8,460	10,791	1.34 (1.23-1.46)	1.26 (1.19-1.33)	1,411	4,879	1.28 (1.13-1.45)	1.23 (1.15-1.30)
P for heterogeneity[c]			*0.024*				*0.026*	
Small Cell Lung Cancer								
Never	148	3,240	1.00 (Reference)	1.00 (Reference)	13	2,167	1.00 (Reference)	1.00 (Reference)
Ever	1,008	10,791	1.62 (1.30-2.02)	1.60 (1.30-1.96)	65	4,879	2.89 (1.53-5.45)	1.97 (1.30-3.00)
P for heterogeneity[c]			*0.979*				*0.989*	
Adenocarcinoma in situ/ Minimally Invasive Adenocarcinoma								
Never	74	1,520	1.00 (reference)	1.00 (reference)	39	880	1.00 (reference)	1.00 (reference)
Ever	551	5,868	1.54 (1.18-2.00)	1.46 (1.14-1.86)	131	2,144	1.52 (1.03-2.24)	1.37 (0.98-1.93)
P for heterogeneity[c]			*0.008*				*0.005*	

ETS, environmental tobacco smoke; Ca, cases; Co, controls; OR, odds ratio; CI, confidence interval; PL, profile likelihood limits
Study is treated as a random-effect variable.
[a]Odds ratios are adjusted for age, sex, race/ethnicity, smoking status, and pack-years of smoking.
[b]Odds ratios are adjusted for age, sex, and race/ethnicity.
[c]P value for heterogeneity across studies.

Table 3-5. Comparison of small cell lung cancer versus non-small cell lung cancer with respect to their associations with ETS exposure

	All				Never Smokers			
Histological Type	**Ca, N**	**Co, N**	**OR (95% CI)[a]**	**ROR (95% CI)[a,c]**	**Ca, N**	**Co, N**	**OR (95% CI)[b]**	**ROR (95% CI)[b,c]**
Non-small cell lung cancer	9,938	14,031	1.34 (1.23-1.46)	1.00 (Reference)	1,931	7,046	1.28 (1.13-1.45)	1.00 (Reference)
Small cell lung cancer	1,156	14,031	1.62 (1.30-2.02)	1.27 (1.02-1.57)	78	7,046	2.89 (1.53-5.45)	2.08 (1.10-3.94)
				P=0.032				P=0.024

ETS, environmental tobacco smoke; Ca, cases; Co, controls; OR, odds ratio; CI, confidence interval; PL, profile likelihood limits; ROR, ratio of odds ratios

All 18 studies included; study is treated as a random-effect variable.

[a]Odds ratios are adjusted for age, sex, race/ethnicity, smoking status, and pack-years of smoking.

[b]Odds ratios are adjusted for age, sex, and race/ethnicity.

[c]Ratio of odds ratios using the case-only study method.

Table 3-6. Associations between location of ETS exposure and lung cancer by histological type

ETS Exposure Location	All			Never Smokers		
	Ca, N	Co, N	OR (95% CI)[a]	Ca, N	Co, N	OR (95% CI)[b]
All Histological Types						
None	1,870	3,240	1.00 (Reference)	651	2,167	1.00 (Reference)
Home	2,217	2,978	1.19 (1.08-1.31)	626	1,712	1.21 (1.05-1.39)
Workplace	1,957	2,857	1.02 (0.92-1.12)	409	1,397	1.10 (0.95-1.29)
Home and workplace	5,212	4,691	1.38 (1.27-1.51)	602	1,654	1.29 (1.12-1.50)
P for heterogeneity[c]			*<0.001*			*<0.001*
Adenocarcinoma						
None	904	3,240	1.00 (Reference)	422	2,167	1.00 (Reference)
Home	1,125	2,978	1.20 (1.07-1.35)	405	1,712	1.21 (1.02-1.42)
Workplace	859	2,857	1.00 (0.89-1.13)	215	1,397	1.00 (0.83-1.21)
Home and workplace	2,449	4,691	1.39 (1.25-1.54)	386	1,654	1.25 (1.05-1.48)
P for heterogeneity[c]			*<0.001*			*<0.001*
Squamous Cell Carcinoma						
None	425	3,240	1.00 (Reference)	52	2,167	1.00 (Reference)
Home	390	2,978	1.16 (0.97-1.40)	49	1,712	1.21 (0.79-1.85)
Workplace	405	2,857	0.95 (0.79-1.14)	41	1,397	1.12 (0.72-1.74)
Home and workplace	1,111	4,691	1.50 (1.27-1.77)	61	1,654	1.83 (1.22-2.74)
P for heterogeneity[c]			*<0.001*			*0.022*
Large Cell Lung Cancer						
None	75	3,240	1.00 (Reference)	22	2,167	1.00 (Reference)
Home	127	2,978	1.28 (0.94-1.75)	26	1,712	1.29 (0.72-2.33)
Workplace	101	2,857	0.97 (0.69-1.38)	17	1,397	1.47 (0.75-2.88)
Home and workplace	310	4,691	1.60 (1.19-2.15)	23	1,654	1.52 (0.81-2.85)
P for heterogeneity[c]			*0.162*			*0.301*
Non-Small Cell Lung Cancer						
None	1,478	3,240	1.00 (Reference)	520	2,167	1.00 (Reference)
Home	1,762	2,978	1.18 (1.07-1.31)	500	1,712	1.19 (1.02-1.38)
Workplace	1,476	2,857	1.00 (0.90-1.11)	288	1,397	1.04 (0.87-1.23)
Home and workplace	4,194	4,691	1.40 (1.27-1.54)	486	1,654	1.30 (1.11-1.52)
P for heterogeneity[c]			*<0.001*			*<0.001*
Small Cell Lung Cancer						
None	148	3,240	1.00 (Reference)	13	2,167	1.00 (Reference)
Home	184	2,978	1.37 (1.05-1.79)	20	1,712	2.92 (1.37-6.21)
Workplace	185	2,857	1.14 (0.86-1.50)	17	1,397	2.11 (0.97-4.56)
Home and workplace	514	4,691	1.65 (1.30-2.10)	25	1,654	3.26 (1.61-6.61)
P for heterogeneity[c]			*0.059*			*0.999*
Adenocarcinoma in situ/ Minimally Invasive Adenocarcinoma						
None	74	1,520	1.00 (Reference)	39	880	1.00 (Reference)
Home	129	1,549	1.27 (0.93-1.73)	46	713	1.34 (0.85-2.11)
Workplace	83	1,708	1.08 (0.78-1.51)	27	680	1.10 (0.66-1.84)
Home and workplace	252	2,447	1.41 (1.04-1.90)	41	721	1.35 (0.84-2.16)
P for heterogeneity[c]			*0.001*			*0.048*

ETS, environmental tobacco smoke; Ca, cases; Co, controls; OR, odds ratio; CI, confidence interval
All 18 studies included; study is treated as a random-effect variable.
[a]Odds ratios are adjusted for age, sex, race/ethnicity, smoking status, and pack-years of smoking.
[b]Odds ratios are adjusted for age, sex, and race/ethnicity.
[c]P value for heterogeneity across studies.

Table 3-7. Associations between duration of ETS exposure at home and lung cancer by histological type

ETS Exposure Duration at Home (Years)	All			Never Smokers		
	Ca, N	Co, N	OR (95% CI)[a]	Ca, N	Co, N	OR (95% CI)[b]
All Histological Types						
0	483	857	1.00 (Reference)	154	514	1.00 (Reference)
1-20	1,396	2,284	1.12 (0.93-1.34)	287	1,024	1.23 (0.93-1.63)
> 20	1,444	1,508	1.38 (1.16-1.63)	233	623	1.20 (0.91-1.57)
P for trend			*< 0.001*			*0.268*
P for heterogeneity[c]			*0.264*			*< 0.001*
Adenocarcinoma						
0	239	857	1.00 (Reference)	83	514	1.00 (Reference)
1-20	625	2,284	1.07 (0.86-1.34)	155	1,024	1.16 (0.82-1.64)
> 20	636	1,508	1.35 (1.10-1.66)	132	623	1.17 (0.84-1.64)
P for trend			*< 0.001*			*0.394*
P for heterogeneity[c]			*0.892*			*< 0.001*
Squamous Cell Carcinoma						
0	102	857	1.00 (Reference)	19	514	1.00 (Reference)
1-20	256	2,284	0.98 (0.69-1.38)	33	1,024	1.75 (0.90-3.39)
> 20	276	1,508	1.23 (0.90-1.69)	30	623	1.67 (0.88-3.17)
P for trend			*0.053*			*0.152*
P for heterogeneity[c]			*0.738*			*0.436*
Large Cell Lung Cancer						
0	18	857	1.00 (Reference)	9	514	1.00 (Reference)
1-20	114	2,284	1.00 (0.52-1.92)	15	1,024	0.64 (0.22-1.84)
> 20	71	1,508	1.54 (0.84-2.84)	11	623	0.89 (0.34-2.32)
P for trend			*0.024*			*0.923*
P for heterogeneity[c]			*0.396*			*0.545*
Non-Small Cell Lung Cancer						
0	375	857	1.00 (Reference)	112	514	1.00 (Reference)
1-20	1,072	2,284	1.09 (0.90-1.33)	211	1,024	1.17 (0.86-1.60)
> 20	1,078	1,508	1.35 (1.12-1.62)	174	623	1.18 (0.87-1.59)
P for trend			*< 0.001*			*0.340*
P for heterogeneity[c]			*0.703*			*< 0.001*
Small Cell Lung Cancer						
0	9	857	1.00 (Reference)	4	514	1.00 (Reference)
1-20	132	2,284	1.56 (0.70-3.47)	13	1,024	1.98 (0.59-6.71)
> 20	124	1,508	2.43 (1.11-5.28)	11	623	2.48 (0.75-8.18)
P for trend			*0.001*			*0.141*
P for heterogeneity[c]			*0.839*			*0.954*
Minimally Invasive Adenocarcinoma/Adenocarcinoma in situ						
0	27	767	1.00 (Reference)	14	464	1.00 (Reference)
1-20	69	1,393	1.45 (0.88-2.37)	28	609	1.78 (0.91-3.49)
> 20	62	719	1.69 (1.04-2.76)	19	335	1.45 (0.71-2.97)
P for trend			*0.037*			*0.302*
P for heterogeneity[c]			*0.809*			*0.827*

ETS, environmental tobacco smoke; Ca, cases; Co, controls; OR, odds ratio; CI, confidence interval
Based on 10 studies: FHS, UCLA, NELCS, SLRI, Moffitt, GenAir, CREST, Liverpool, IARC, and Hawaii
Study is treated as a random-effect variable.
[a]Odds ratios are adjusted for age, sex, race/ethnicity, smoking status, and pack-years of smoking.
[b]Odds ratios are adjusted for age, sex, and race/ethnicity.
[c]P value for heterogeneity across studies.

Table 3-8. Associations between duration of ETS exposure at work and lung cancer by histological type

ETS Exposure Duration at Work (Years)	All			Never Smokers		
	Ca, N	Co, N	OR (95% CI)[a]	Ca, N	Co, N	OR (95% CI)[b]
All Histological Types						
0	688	1,388	1.00 (Reference)	283	875	1.00 (Reference)
1-20	1,506	2,508	1.03 (0.89-1.19)	291	1,168	1.09 (0.88-1.36)
> 20	1,333	1,590	1.20 (1.04-1.39)	193	611	1.23 (0.96-1.57)
P for trend			*0.008*			*0.102*
P for heterogeneity[c]			*0.032*			*0.001*
Adenocarcinoma						
0	331	1,388	1.00 (Reference)	153	875	1.00 (Reference)
1-20	703	2,508	1.01 (0.84-1.21)	144	1,168	1.02 (0.76-1.35)
> 20	530	1,590	1.21 (1.00-1.46)	103	611	1.31 (0.96-1.78)
P for trend			*0.034*			*0.102*
P for heterogeneity[c]			*0.215*			*0.032*
Squamous Cell Carcinoma						
0	109	1,388	1.00 (Reference)	26	875	1.00 (Reference)
1-20	208	2,508	1.01 (0.75-1.37)	30	1,168	1.58 (0.85-2.92)
> 20	321	1,590	1.39 (1.05-1.84)	38	611	1.93 (1.09-3.43)
P for trend			*0.005*			*0.026*
P for heterogeneity[c]			*0.026*			*0.160*
Large Cell Lung Cancer						
0	31	1,388	1.00 (Reference)	12	875	1.00 (Reference)
1-20	128	2,508	1.30 (0.80-2.12)	24	1,168	2.05 (0.91-4.63)
> 20	54	1,590	1.06 (0.64-1.77)	2	611	0.29 (0.06-1.37)
P for trend			*0.985*			*0.364*
P for heterogeneity[c]			*0.636*			*0.797*
Non-Small Cell Lung Cancer						
0	501	1,388	1.00 (Reference)	196	875	1.00 (Reference)
1-20	1,137	2,508	1.06 (0.90-1.24)	207	1,168	1.18 (0.91-1.52)
> 20	983	1,590	1.21 (1.03-1.43)	143	611	1.30 (0.99-1.72)
P for trend			*0.013*			*0.056*
P for heterogeneity[c]			*0.138*			*0.013*
Small Cell Lung Cancer						
0	28	1,388	1.00 (Reference)	7	875	1.00 (Reference)
1-20	133	2,508	1.05 (0.64-1.74)	16	1,168	1.70 (0.65-4.49)
> 20	131	1,590	1.43 (0.87-2.37)	12	611	2.17 (0.78-6.03)
P for trend			*0.057*			*0.137*
P for heterogeneity[c]			*0.432*			*0.999*
Minimally Invasive Adenocarcinoma/Adenocarcinoma in situ						
0	27	767	1.00 (Reference)	14	464	1.00 (Reference)
1-20	69	1,393	1.45 (0.88-2.37)	28	609	1.78 (0.91-3.49)
> 20	62	719	1.69 (1.04-2.76)	19	335	1.45 (0.71-2.97)
P for trend			0.037			0.302
P for heterogeneity[c]			*0.809*			*0.827*

ETS, environmental tobacco smoke; Ca, cases; Co, controls; OR, odds ratio; CI, confidence interval
Based on 10 studies: FHS, UCLA, NELCS, SLRI, Moffitt, GenAir, CREST, Liverpool, IARC, and Hawaii
Study is treated as a random-effect variable.
[a]Odds ratios are adjusted for age, sex, race/ethnicity, smoking status, and pack-years of smoking.
[b]Odds ratios are adjusted for age, sex, and race/ethnicity.
[c]P value for heterogeneity across studies.

Table 3-9. Associations between duration of ETS exposure at home and work and lung cancer by histological type

Combined ETS Exposure Duration at Home and Work (Years)	All			Never Smokers		
	Ca, N	Co, N	OR (95% CI)[a]	Ca, N	Co, N	OR (95% CI)[b]
All Histological Types						
0	231	517	1.00 (Reference)	80	315	1.00 (Reference)
1-20	488	1,019	0.94 (0.74-1.19)	160	557	1.13 (0.79-1.61)
21-40	760	1,024	1.12 (0.89-1.42)	173	446	1.32 (0.93-1.87)
> 40	978	983	1.25 (0.99-1.59)	135	312	1.34 (0.93-1.93)
P for trend			*0.002*			*0.066*
P for heterogeneity[c]			*0.006*			*0.022*
Adenocarcinoma						
0	121	517	1.00 (Reference)	51	315	1.00 (Reference)
1-20	262	1,019	0.87 (0.65-1.17)	80	557	0.90 (0.58-1.38)
21-40	352	1,024	0.99 (0.75-1.31)	93	446	1.15 (0.76-1.74)
> 40	410	983	1.11 (0.83-1.49)	71	312	1.18 (0.76-1.83)
P for trend			*0.109*			*0.208*
P for heterogeneity[c]			*0.004*			*0.071*
Squamous Cell Carcinoma						
0	47	517	1.00 (Reference)	9	315	1.00 (Reference)
1-20	51	1,019	0.69 (0.42-1.14)	11	557	1.21 (0.46-3.18)
21-40	128	1,024	1.17 (0.75-1.80)	21	446	1.96 (0.83-4.59)
> 40	204	983	1.29 (0.84-1.99)	29	312	2.84 (1.25-6.45)
P for trend			*0.009*			*0.003*
P for heterogeneity[c]			*0.072*			*0.443*
Large Cell Lung Cancer						
0	10	517	1.00 (Reference)	5	315	1.00 (Reference)
1-20	33	1,019	0.56 (0.24-1.30)	8	557	0.78 (0.23-2.68)
21-40	53	1,024	0.79 (0.35-1.77)	11	446	1.24 (0.40-3.89)
> 40	40	983	1.01 (0.44-2.31)	4	312	0.71 (0.18-2.76)
P for trend			*0.170*			*0.966*
P for heterogeneity[c]			*0.973*			*0.999*
Non-Small Cell Lung Cancer						
0	181	517	1.00 (Reference)	65	315	1.00 (Reference)
1-20	385	1,019	0.85 (0.66-1.11)	106	557	0.93 (0.63-1.38)
21-40	577	1,024	1.03 (0.80-1.32)	127	446	1.20 (0.83-1.75)
> 40	741	983	1.17 (0.91-1.51)	105	312	1.30 (0.88-1.93)
P for trend			*0.010*			*0.052*
P for heterogeneity[c]			*0.001*			*0.034*
Small Cell Lung Cancer						
0	6	517	1.00 (Reference)	1	315	1.00 (Reference)
1-20	26	1,019	1.31 (0.47-3.60)	7	557	4.01 (0.46-34.82)
21-40	68	1,024	2.02 (0.78-5.24)	7	446	4.23 (0.50-35.78)
> 40	91	983	2.35 (0.92-6.01)	6	312	4.99 (0.58-42.77)
P for trend			*0.010*			*0.170*
P for heterogeneity[c]			*0.960*			*1.000*

Table 3-9. Associations between duration of ETS exposure at home and work and lung cancer by histological type

Combined ETS Exposure Duration at Home and Work (Years)	All			Never Smokers		
	Ca, N	Co, N	OR (95% CI)[a]	Ca, N	Co, N	OR (95% CI)[b]
Adenocarcinoma in situ/Minimally Invasive Adenocarcinoma						
0	9	436	1.00 (Reference)	6	274	1.00 (Reference)
1-20	29	676	1.63 (0.73-3.63)	14	363	1.82 (0.67-4.91)
21-40	41	634	2.21 (1.02-4.77)	18	282	3.01 (1.16-7.84)
> 40	37	394	2.35 (1.06-5.20)	8	170	1.88 (0.63-5.60)
P for trend			0.023			0.096
P for heterogeneity[c]			*0.088*			*0.151*

ETS, environmental tobacco smoke; Ca, cases; Co, controls; OR, odds ratio; CI, confidence interval
Based on 10 studies: FHS, UCLA, NELCS, SLRI, Moffitt, GenAir, CREST, Liverpool, IARC, and Hawaii
Study is treated as a random-effect variable.
[a]Odds ratios are adjusted for age, sex, race/ethnicity, smoking status, and pack-years of smoking.
[b]Odds ratios are adjusted for age, sex, and race/ethnicity.
[c]P value for heterogeneity across studies.

Table 3-10. Associations between ETS exposure in childhood and lung cancer by histological type

ETS Exposure in Childhood	All			Never Smokers		
	Ca, N	Co, N	OR (95% CI)[a]	Ca, N	Co, N	OR (95% CI)[b]
All Histological Types						
Never	2,081	2,071	1.00 (Reference)	485	1,077	1.00 (Reference)
Ever	4,153	3,736	1.16 (1.06-1.26)	562	1,601	1.09 (0.93-1.27)
P for heterogeneity[c]			*0.663*			*0.293*
Adenocarcinoma						
Never	1,029	2,071	1.00 (Reference)	318	1,077	1.00 (Reference)
Ever	1,813	3,736	1.11 (1.00-1.23)	304	1,601	0.99 (0.82-1.19)
P for heterogeneity[c]			*0.788*			*0.491*
Squamous Cell Carcinoma						
Never	420	2,071	1.00 (Reference)	26	1,077	1.00 (Reference)
Ever	822	3,736	1.11 (0.95-1.31)	35	1,601	1.07 (0.63-1.82)
P for heterogeneity[c]			*0.911*			*0.646*
Large Cell Lung Cancer						
Never	80	2,071	1.00 (Reference)	12	1,077	1.00 (Reference)
Ever	229	3,736	1.17 (0.89-1.55)	20	1,601	1.43 (0.68-3.01)
P for heterogeneity[c]			*0.231*			*0.592*
Non-Small Cell Lung Cancer						
Never	1,701	2,071	1.00 (Reference)	393	1,077	1.00 (Reference)
Ever	3,196	3,736	1.13 (1.03-1.24)	379	1,601	0.98 (0.83-1.17)
P for heterogeneity[c]			*0.704*			*0.425*
Small Cell Lung Cancer						
Never	159	2,071	1.00 (Reference)	8	1,077	1.00 (Reference)
Ever	457	3,736	1.35 (1.09-1.68)	17	1,601	1.62 (0.68-3.83)
P for heterogeneity[c]			*0.916*			*0.629*
Adenocarcinoma in situ/Minimally Invasive Adenocarcinoma						
Never	117	1,579	1.00 (Reference)	45	744	1.00 (Reference)
Ever	177	2,378	1.17 (0.91-1.51)	41	809	1.03 (0.66-1.60)
P for heterogeneity[c]			*0.033*			*0.021*

ETS, environmental tobacco smoke; Ca, cases; Co, controls; OR, odds ratio; CI, confidence interval
Based on 7 studies: FHS, UCLA, NELCS, SLRI, Mayo, Moffitt, and GenAir
Study is treated as a random-effect variable.
[a]Odds ratios are adjusted for age, sex, race/ethnicity, smoking status, and pack-years of smoking.
[b]Odds ratios are adjusted for age, sex, and race/ethnicity.
[c]P value for heterogeneity across studies.

Table 3-11. Distribution of characteristics of lung cancer cases and controls in ILCCO studies pooled for analyses of DNA repair, carcinogen metabolism, and cell cycle control gene variants

	Cases, n	(%)	Controls, n	(%)	P[a]
Total	745		2,606		<0.001
Study					
IARC	167	(22.4)	717	(27.5)	
Harvard	149	(20.0)	454	(17.4)	
Seoul	129	(17.3)	217	(8.3)	
GEL-S	104	(14.0)	162	(6.2)	
UCLA	86	(11.5)	408	(15.7)	
Kyushu	59	(7.9)	57	(2.2)	
GenAir	51	(6.8)	591	(22.7)	
Age (years)					<0.001
<50	140	(18.8)	596	(22.9)	
50-59	183	(24.6)	814	(31.2)	
60-69	220	(29.5)	727	(27.9)	
70-79	159	(21.3)	431	(16.5)	
≥80	43	(5.8)	38	(1.5)	
Mean (SD)	61.1	(12.0)	58.1	(11.4)	
Sex					
Male	165	(22.1)	1,118	(42.9)	<0.001
Female	580	(77.9)	1,488	(57.1)	
Race/ethnicity					
Non-Hispanic white	393	(52.8)	2,021	(77.6)	<0.001
Asian	315	(42.3)	463	(17.8)	
Hispanic or Latino	27	(3.6)	81	(3.1)	
Black/African-American	8	(1.1)	30	(1.2)	
Other	2	(0.3)	11	(0.4)	
Histology					
Adenocarcinoma	446	(59.9)			
Squamous cell carcinoma	90	(12.1)			
Large cell lung cancer	42	(5.6)			
Unspecified non-small cell lung cancer	5	(0.7)			
Small cell lung cancer	38	(5.1)			
Other/mixed/unknown	124	(16.6)			

[a]P-value for $\chi 2$-tests comparing cases and controls.

Table 3-12. Associations between polymorphisms of DNA repair, carcinogen metabolism, and cell cycle control genes and lung cancer in never smokers by ETS exposure status

	All			Unexposed to ETS			Exposed to ETS		
Gene variant dbSNP no.	**Ca/Co[a]**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**	**Ca/Co**	**OR[c] (95% CI)**	**Bayesian Posterior OR[c] (95% CI)**	**Ca/Co**	**OR[c] (95% CI)**	**Bayesian Posterior OR[c] (95% CI)**
DNA repair pathway									
APEX1 D148E rs3136820	Studies included: IARC, Harvard, and GenAir								
TT	107/445	1.00 (Reference)	1.00 (Reference)	16/59	1.00 (Reference)	1.00 (Reference)	68/232	1.00 (Reference)	1.00 (Reference)
TG	164/873	0.88 (0.64-1.20)	0.88 (0.65-1.19)	26/137	0.89 (0.43-1.85)	0.93 (0.52-1.66)	115/477	0.87 (0.61-1.23)	0.88 (0.64-1.23)
GG	85/398	1.06 (0.73-1.54)	1.06 (0.74-1.51)	15/54	1.26 (0.54-2.90)	1.14 (0.61-2.14)	55/210	1.03 (0.68-1.56)	1.03 (0.70-1.50)
P_{trend}		*0.810*	*0.812*		*0.612*	*0.640*		*0.944*	*0.945*
OGG1 S326C rs1052133	Studies included: IARC and GenAir								
CC	127/813	1.00 (Reference)	1.00 (Reference)	32/144	1.00 (Reference)	1.00 (Reference)	62/335	1.00 (Reference)	1.00 (Reference)
CG	76/423	1.32 (0.90-1.91)	1.29 (0.90-1.85)	13/74	0.87 (0.42-1.80)	0.91 (0.51-1.62)	47/165	1.53 (0.98-2.38)	1.42 (0.95-2.13)
GG	15/61	1.81 (0.91-3.59)	1.61 (0.88-2.97)	4/14	1.07 (0.31-3.77)	1.03 (0.48-2.20)	10/22	2.24 (0.97-5.15)	1.61 (0.85-3.02)
P_{trend}		*0.044*	*0.048*		*0.881*	*0.893*		*0.015*	*0.021*
XRCC1 R194W rs1799782	Studies included: IARC and GenAir								
CC	180/1,127	1.00 (Reference)	1.00 (Reference)	39/194	1.00 (Reference)	1.00 (Reference)	102/455	1.00 (Reference)	1.00 (Reference)
CT	30/169	0.86 (0.50-1.49)	0.88 (0.53-1.46)	7/41	0.75 (0.30-1.86)	0.85 (0.44-1.65)	12/63	0.99 (0.50-1.97)	0.99 (0.57-1.73)
TT	4/8	6.00 (1.46-24.64)	2.48 (0.91-6.77)	1/2	3.86 (0.27-54.65)	1.23 (0.49-3.07)	3/4	7.36 (1.36-39.74)	1.66 (0.69-4.00)
P_{trend}		*0.448*	0.*468*		*0.896*	*0.917*		*0.236*	*0.296*
XRCC1 R399Q rs25487	Studies included: IARC, Harvard, Kyushu, and GenAir								
CC	191/793	1.00 (Reference)	1.00 (Reference)	33/117	1.00 (Reference)	1.00 (Reference)	132/438	1.00 (Reference)	1.00 (Reference)
CT	175/767	0.95 (0.72-1.24)	0.95 (0.73-1.24)	19/102	0.71 (0.36-1.37)	0.79 (0.46-1.35)	124/420	0.98 (0.72-1.32)	0.98 (0.74-1.31)
TT	49/214	1.22 (0.81-1.83)	1.20 (0.82-1.77)	7/30	1.09 (0.41-2.86)	1.04 (0.53-2.06)	36/118	1.23 (0.78-1.93)	1.19 (0.79-1.78)
P_{trend}		*0.578*	0.*581*		*0.713*	*0.736*		*0.537*	*0.545*
XRCC2 R188H rs3218536	Studies included: IARC and GenAir								
GG	172/1,007	1.00 (Reference)	1.00 (Reference)	43/206	1.00 (Reference)	1.00 (Reference)	98/456	1.00 (Reference)	1.00 (Reference)
GA	30/153	1.35 (0.79-2.29)	1.30 (0.79-2.12)	5/28	0.82 (0.29-2.38)	0.91 (0.45-1.85)	17/56	1.57 (0.84-2.92)	1.38 (0.82-2.33)
AA	2/4	1.10 (0.11-11.40)	1.03 (0.33-3.22)	0/0			1/3	1.05 (0.10-11.00)	1.01 (0.42-2.44)
P_{trend}		*0.306*	0.*330*					*0.217*	*0.277*

Table 3-12. Associations between polymorphisms of DNA repair, carcinogen metabolism, and cell cycle control genes and lung cancer in never smokers by ETS exposure status

	All			Unexposed to ETS			Exposed to ETS		
Gene variant dbSNP no.	**Ca/Co[a]**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**	**Ca/Co**	**OR[c] (95% CI)**	**Bayesian Posterior OR[c] (95% CI)**	**Ca/Co**	**OR[c] (95% CI)**	**Bayesian Posterior OR[c] (95% CI)**
XRCC3 T241M rs861539	Studies included: IARC, GEL-S, Kyushu, and GenAir								
GG	208/655	1.00 (Reference)	1.00 (Reference)	46/144	1.00 (Reference)	1.00 (Reference)	131/303	1.00 (Reference)	1.00 (Reference)
GA	121/637	1.14 (0.80-1.63)	1.13 (0.81-1.59)	24/112	1.09 (0.56-2.12)	1.06 (0.62-1.83)	74/258	1.16 (0.76-1.76)	1.13 (0.77-1.66)
AA	40/196	1.29 (0.77-2.15)	1.25 (0.78-2.01)	12/28	2.15 (0.90-5.13)	1.54 (0.81-2.95)	18/87	1.03 (0.54-1.95)	1.02 (0.60-1.74)
P_{trend}		*0.297*	0.303		*0.138*	*0.171*		*0.728*	*0.738*
ERCC1 T354C rs11615	Studies included: IARC, Harvard, and GenAir								
TT	133/663	1.00 (Reference)	1.00 (Reference)	28/110	1.00 (Reference)	1.00 (Reference)	80/347	1.00 (Reference)	1.00 (Reference)
CT	158/799	1.00 (0.75-1.34)	1.00 (0.75-1.33)	24/108	0.85 (0.45-1.62)	0.89 (0.53-1.52)	107/437	1.05 (0.76-1.47)	1.05 (0.77-1.43)
CC	67/267	1.40 (0.96-2.04)	1.37 (0.95-1.97)	5/32	0.85 (0.29-2.54)	0.93 (0.45-1.90)	52/147	1.56 (1.03-2.35)	1.46 (1.00-2.13)
P_{trend}		*0.142*	0.*145*		*0.646*	*0.677*		*0.057*	*0.062*
ERCC1 C8092A rs3212986	Studies included: IARC and Harvard								
CC	165/639	1.00 (Reference)	1.00 (Reference)	37/153	1.00 (Reference)	1.00 (Reference)	114/447	1.00 (Reference)	1.00 (Reference)
CA	117/435	1.08 (0.81-1.44)	1.08 (0.81-1.42)	15/81	0.87 (0.44-1.73)	0.91 (0.52-1.59)	94/333	1.14 (0.83-1.57)	1.13 (0.84-1.52)
AA	25/72	1.37 (0.81-2.30)	1.32 (0.81-2.13)	1/12	0.63 (0.07-5.28)	0.90 (0.38-2.16)	22/56	1.55 (0.89-2.67)	1.40 (0.87-2.24)
P_{trend}		*0.272*	0.277		*0.586*	*0.637*		*0.123*	*0.133*
ERCC2/XPD D312N rs1799793	Studies included: IARC, Harvard, and GenAir								
GG	128/667	1.00 (Reference)	1.00 (Reference)	20/95	1.00 (Reference)	1.00 (Reference)	84/371	1.00 (Reference)	1.00 (Reference)
AG	162/786	1.09 (0.82-1.47)	1.09 (0.82-1.45)	29/112	1.18 (0.61-2.28)	1.12 (0.65-1.93)	102/419	1.06 (0.76-1.47)	1.05 (0.77-1.44)
AA	65/264	1.46 (0.99-2.13)	1.42 (0.98-2.05)	5/34	0.83 (0.28-2.49)	0.92 (0.45-1.88)	51/136	1.59 (1.05-2.40)	1.48 (1.01-2.16)
P_{trend}		*0.073*	0.075		*0.978*	*0.980*		*0.050*	*0.055*
ERCC2/XPD K751Q rs13181	Studies included: IARC, Harvard, GEL-S, Kyushu, and GenAir								
AA	253/801	1.00 (Reference)	1.00 (Reference)	52/146	1.00 (Reference)	1.00 (Reference)	163/454	1.00 (Reference)	1.00 (Reference)
AC	203/868	0.97 (0.74-1.25)	0.97 (0.75-1.25)	32/126	1.05 (0.58-1.89)	1.04 (0.63-1.71)	141/490	0.94 (0.70-1.26)	0.95 (0.71-1.25)
CC	67/298	1.17 (0.81-1.70)	1.16 (0.81-1.66)	8/40	1.02 (0.40-2.55)	1.01 (0.52-1.96)	48/151	1.21 (0.80-1.83)	1.18 (0.81-1.72)
P_{trend}		*0.572*	0.*575*		*0.921*	*0.927*		*0.555*	*0.563*

Table 3-12. Associations between polymorphisms of DNA repair, carcinogen metabolism, and cell cycle control genes and lung cancer in never smokers by ETS exposure status

	All			Unexposed to ETS			Exposed to ETS		
Gene variant dbSNP no.	**Ca/Co[a]**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**	**Ca/Co**	**OR[c] (95% CI)**	**Bayesian Posterior OR[c] (95% CI)**	**Ca/Co**	**OR[c] (95% CI)**	**Bayesian Posterior OR[c] (95% CI)**
XPG H1104D rs17655	Studies included: IARC and UCLA								
CC	138/638	1.00 (Reference)	1.00 (Reference)	42/228	1.00 (Reference)	1.00 (Reference)	90/377	1.00 (Reference)	1.00 (Reference)
GC	97/391	1.21 (0.89-1.65)	1.20 (0.89-1.62)	37/138	1.71 (1.03-2.86)	1.53 (0.97-2.40)	54/230	0.99 (0.67-1.46)	0.99 (0.69-1.42)
GG	15/84	0.94 (0.52-1.73)	0.95 (0.55-1.65)	2/29	0.40 (0.09-1.81)	0.75 (0.33-1.69)	13/51	1.21 (0.61-2.39)	1.14 (0.65-1.98)
P_{trend}		*0.539*	0.*544*		*0.543*	*0.571*		*0.735*	*0.745*
Carcinogen metabolism pathway									
CYP1A1 I462V rs1048943	Studies included: IARC, GEL-S, and Kyushu								
AA	255/759	1.00 (Reference)	1.00 (Reference)	61/242	1.00 (Reference)	1.00 (Reference)	171/456	1.00 (Reference)	1.00 (Reference)
AG	51/125	0.69 (0.45-1.05)	0.71 (0.48-1.07)	11/35	0.70 (0.31-1.56)	0.80 (0.43-1.49)	38/82	0.69 (0.42-1.14)	0.74 (0.48-1.16)
GG	17/12	1.42 (0.59-3.44)	1.29 (0.62-2.68)	5/3	2.84 (0.62-13.12)	1.39 (0.61-3.16)	10/8	0.93 (0.31-2.80)	0.97 (0.47-1.99)
P_{trend}		*0.482*	0.*492*		*0.73*	*0.762*		*0.268*	*0.302*
CYP1A1 T3801C rs4646903	Studies included: IARC, GEL-S, and Kyushu								
TT	178/619	1.00 (Reference)	1.00 (Reference)	45/185	1.00 (Reference)	1.00 (Reference)	118/380	1.00 (Reference)	1.00 (Reference)
CT	108/241	0.78 (0.54-1.13)	0.80 (0.56-1.13)	26/81	0.68 (0.35-1.31)	0.76 (0.44-1.31)	73/147	0.83 (0.54-1.29)	0.86 (0.58-1.28)
CC	34/50	0.89 (0.48-1.64)	0.90 (0.52-1.58)	7/10	1.08 (0.33-3.60)	1.03 (0.49-2.18)	24/38	0.83 (0.40-1.73)	0.89 (0.50-1.58)
P_{trend}		*0.358*	0.366		*0.568*	*0.610*		*0.461*	*0.483*
GSTM1	Studies included: IARC, GEL-S, and Kyushu								
Present	147/440	1.00 (Reference)	1.00 (Reference)	38/144	1.00 (Reference)	1.00 (Reference)	95/263	1.00 (Reference)	1.00 (Reference)
Null	170/430	1.04 (0.78-1.40)	1.04 (0.78-1.39)	41/122	1.21 (0.71-2.07)	1.16 (0.73-1.85)	117/274	0.97 (0.68-1.39)	0.98 (0.70-1.36)
GSTT1	Studies included: IARC, GEL-S, and Kyushu								
Present	219/670	1.00 (Reference)	1.00 (Reference)	54/204	1.00 (Reference)	1.00 (Reference)	146/411	1.00 (Reference)	1.00 (Reference)
Null	104/221	1.00 (0.71-1.41)	1.00 (0.72-1.39)	26/69	0.98 (0.53-1.81)	0.99 (0.59-1.65)	71/139	0.98 (0.64-1.50)	0.98 (0.67-1.45)
GSTP1 I105V rs947894	Studies included: IARC and Kyushu								
AA	123/374	1.00 (Reference)	1.00 (Reference)	25/115	1.00 (Reference)	1.00 (Reference)	90/233	1.00 (Reference)	1.00 (Reference)
AG	81/324	1.04 (0.72-1.51)	1.04 (0.73-1.49)	19/97	1.05 (0.53-2.10)	1.04 (0.59-1.81)	59/196	1.02 (0.66-1.59)	1.02 (0.68-1.52)
GG	18/63	1.16 (0.62-2.18)	1.13 (0.64-2.00)	5/22	1.23 (0.40-3.75)	1.10 (0.53-2.27)	12/39	1.11 (0.52-2.38)	1.07 (0.59-1.94)
P_{trend}		*0.657*	0.*662*		*0.733*	*0.758*		*0.815*	*0.824*

Table 3-12. Associations between polymorphisms of DNA repair, carcinogen metabolism, and cell cycle control genes and lung cancer in never smokers by ETS exposure status

	All			Unexposed to ETS			Exposed to ETS		
Gene variant dbSNP no.	**Ca/Co[a]**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**	**Ca/Co**	**OR[c] (95% CI)**	**Bayesian Posterior OR[c] (95% CI)**	**Ca/Co**	**OR[c] (95% CI)**	**Bayesian Posterior OR[c] (95% CI)**
ATM C77T rs664677	Studies included: IARC and Seoul								
TT	69/236	1.00 (Reference)	1.00 (Reference)	21/66	1.00 (Reference)	1.00 (Reference)	37/129	1.00 (Reference)	1.00 (Reference)
TC	152/450	0.96 (0.65-1.40)	0.96 (0.66-1.38)	46/146	0.86 (0.45-1.62)	0.90 (0.53-1.52)	82/229	1.02 (0.63-1.65)	1.02 (0.66-1.56)
CC	72/234	0.65 (0.41-1.05)	0.68 (0.44-1.06)	18/78	0.54 (0.25-1.16)	0.68 (0.37-1.24)	36/92	0.68 (0.37-1.26)	0.76 (0.45-1.27)
P_{trend}		*0.081*	0.084		*0.109*	*0.133*		*0.249*	*0.268*
Cell cycle pathway									
TP53 R72P rs1042522	Studies included: IARC, Harvard, and UCLA								
GG	127/672	1.00 (Reference)	1.00 (Reference)	40/132	1.00 (Reference)	1.00 (Reference)	67/302	1.00 (Reference)	1.00 (Reference)
CG	146/535	1.13 (0.82-1.55)	1.12 (0.82-1.53)	29/122	0.68 (0.38-1.24)	0.76 (0.46-1.25)	88/253	1.39 (0.95-2.04)	1.33 (0.93-1.90)
CC	31/111	0.79 (0.47-1.33)	0.81 (0.50-1.32)	10/29	0.56 (0.23-1.36)	0.72 (0.38-1.39)	15/53	0.92 (0.48-1.77)	0.94 (0.55-1.62)
P_{trend}		*0.735*	0.*738*		*0.133*	*0.164*		*0.526*	*0.540*

ETS, environmental tobacco smoke; Ca, cases; Co, controls; OR, odds ratio; CI, confidence interval

[a]Due to some missing data on ETS exposure status, the total numbers of cases and controls may be greater than the sum of those exposed and unexposed.

[b]Odds ratios adjusted for age, sex, and race/ethnicity, study, and ETS exposure status.

[c]Odds ratios adjusted for age, sex, and race/ethnicity, and study.

Table 3-13. Joint associations of polymorphisms of DNA repair, carcinogen metabolism, and cell cycle control genes and exposure to ETS on lung cancer in never smokers

Genetic Variant dbSNP no.	Unexposed to ETS		Exposed to ETS		Multiplicative Interaction		Additive Interaction
	OR[a] (95% CI)	Bayesian Posterior OR[a] (95% CI)	OR[a] (95% CI)	Bayesian Posterior OR[a] (95% CI)	ROR[a] (95% CI)	Bayesian Posterior ROR[a] (95% CI)	RERI[a] (95% CI)
DNA repair pathway							
APEX1 D148E rs3136820	Studies included: IARC, Harvard, and GenAir						
TT	1.00 (Reference)	1.00 (Reference)	0.99 (0.52-1.89)	1.01 (0.63-1.62)	0.94 (0.45-1.96)	0.95 (0.49-1.82)	-0.06 (-0.82-0.70)
TG + GG	0.98 (0.50-1.91)	1.00 (0.61-1.63)	0.91 (0.50-1.66)	0.93 (0.60-1.44)			
OGG1 S326C rs1052133	Studies included: IARC and GenAir						
CC	1.00 (Reference)	1.00 (Reference)	0.74 (0.45-1.22)	0.77 (0.51-1.17)	1.71 (0.77-3.79)	1.51 (0.76-2.97)	0.51 (-0.18-1.21)
CG + GG	0.94 (0.48-1.85)	0.97 (0.55-1.66)	1.20 (0.72-2.00)	1.20 (0.78-1.84)			
XRCC1 R194W rs1799782	Studies included: IARC and GenAir						
CC	1.00 (Reference)	1.00 (Reference)	0.91 (0.59-1.39)	0.93 (0.64-1.35)	1.48 (0.51-4.33)	1.29 (0.56-2.95)	0.37 (-0.57-1.31)
CT + TT	0.80 (0.34-1.90)	0.88 (0.47-1.67)	1.07 (0.54-2.15)	1.07 (0.61-1.87)			
XRCC1 R399Q rs25487	Studies included: IARC, Harvard, Kyushu, and GenAir						
CC	1.00 (Reference)	1.00 (Reference)	0.89 (0.56-1.43)	0.93 (0.63-1.38)	1.18 (0.61-2.29)	1.15 (0.64-2.07)	0.16 (-0.42-0.73)
CT + TT	0.87 (0.48-1.59)	0.92 (0.56-1.50)	0.92 (0.58-1.47)	0.96 (0.65-1.40)			
XRCC2 R188H rs3218536	Studies included: IARC and GenAir						
GG	1.00 (Reference)	1.00 (Reference)	0.86 (0.56-1.31)	0.86 (0.60-1.25)	1.66 (0.49-5.57)	1.35 (0.55-3.28)	0.53 (-0.67-1.73)
GA + AA	0.92 (0.32-2.63)	0.96 (0.47-1.95)	1.31 (0.68-2.54)	1.22 (0.71-2.11)			
XRCC3 T241M rs861539	Studies included: IARC, GEL−S, Kyushu, and GenAir						
GG	1.00 (Reference)	1.00 (Reference)	0.96 (0.63-1.48)	0.94 (0.65-1.37)	0.89 (0.47-1.66)	0.91 (0.51-1.59)	-0.15 (-0.88-0.59)
GA + AA	1.28 (0.73-2.23)	1.20 (0.75-1.91)	1.09 (0.68-1.75)	1.05 (0.71-1.57)			
ERCC1 T354C rs11615	Studies included: IARC, Harvard, and GenAir						
TT	1.00 (Reference)	1.00 (Reference)	0.76 (0.46-1.27)	0.82 (0.54-1.25)	1.37 (0.70-2.66)	1.29 (0.71-2.34)	0.27 (-0.26-0.80)
TC + CC	0.86 (0.47-1.55)	0.92 (0.57-1.49)	0.89 (0.55-1.44)	0.95 (0.64-1.41)			
ERCC1 C8092A rs3212986	Studies included: IARC and Harvard						
CC	1.00 (Reference)	1.00 (Reference)	0.85 (0.55-1.33)	0.89 (0.61-1.29)	1.49 (0.72-3.05)	1.37 (0.73-2.57)	0.36 (-0.21-0.94)
CA + AA	0.81 (0.42-1.56)	0.87 (0.51-1.48)	1.03 (0.66-1.60)	1.06 (0.72-1.54)			
ERCC2/XPD D312N rs1799793	Studies included: IARC, Harvard, and GenAir						
GG	1.00 (Reference)	1.00 (Reference)	0.93 (0.53-1.65)	0.92 (0.59-1.42)	1.06 (0.53-2.12)	1.04 (0.56-1.93)	0.05 (-0.66-0.76)
GA + AA	1.13 (0.61-2.11)	1.09 (0.67-1.78)	1.11 (0.65-1.91)	1.09 (0.72-1.64)			

Table 3-13. Joint associations of polymorphisms of DNA repair, carcinogen metabolism, and cell cycle control genes and exposure to ETS on lung cancer in never smokers

	Unexposed to ETS		Exposed to ETS		Multiplicative Interaction		Additive Interaction
Genetic Variant dbSNP no.	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**ROR[a] (95% CI)**	**Bayesian Posterior ROR[a] (95% CI)**	**RERI[a] (95% CI)**
ERCC2/XPD K751Q rs13181	Studies included: IARC, Harvard, GEL-S, Kyushu, and GenAir						
AA	1.00 (Reference)	1.00 (Reference)	0.97 (0.66-1.44)	0.97 (0.69-1.37)	0.94 (0.54-1.64)	0.95 (0.57-1.58)	-0.06 (-0.65-0.52)
AC + CC	1.06 (0.64-1.77)	1.05 (0.68-1.63)	0.97 (0.64-1.45)	0.97 (0.68-1.38)			
XPG H1104D rs17655	Studies included: IARC and UCLA						
CC	1.00 (Reference)	1.00 (Reference)	1.11 (0.73-1.68)	1.05 (0.73-1.51)	0.68 (0.36-1.25)	0.72 (0.41-1.26)	-0.49 (-1.44-0.37)
CG +GG	1.51 (0.91-2.48)	1.37 (0.89-2.11)	1.13 (0.73-1.75)	1.07 (0.73-1.56)			
Carcinogen metabolism pathway							
CYP1A1 I462V rs1048943	Studies included: IARC, GEL-S, and Kyushu						
AA	1.00 (Reference)	1.00 (Reference)	1.07 (0.74-1.53)	1.08 (0.78-1.50)	0.83 (0.37-1.86)	0.87 (0.44-1.72)	-0.17 (-0.90-0.57)
AG + GG	0.87 (0.43-1.76)	0.92 (0.53-1.62)	0.77 (0.46-1.29)	0.82 (0.52-1.28)			
CYP1A1 T3801C rs4646903	Studies included: IARC, GEL-S, and Kyushu						
TT	1.00 (Reference)	1.00 (Reference)	0.90 (0.59-1.37)	0.96 (0.66-1.38)	1.06 (0.55-2.04)	1.05 (0.58-1.88)	0.06 (-0.48-0.61)
TC + CC	0.77 (0.43-1.36)	0.85 (0.53-1.36)	0.73 (0.44-1.21)	0.80 (0.52-1.22)			
GSTM1	Studies included: IARC, GEL-S, and Kyushu						
Present	1.00 (Reference)	1.00 (Reference)	1.04 (0.66-1.65)	1.02 (0.69-1.50)	0.81 (0.43-1.53)	0.84 (0.47-1.49)	-0.23 (-0.98-0.52)
Null	1.21 (0.71-2.08)	1.16 (0.74-1.82)	1.02 (0.65-1.61)	1.00 (0.68-1.46)			
GSTT1	Studies included: IARC, GEL-S, and Kyushu						
Present	1.00 (Reference)	1.00 (Reference)	0.97 (0.66-1.43)	0.98 (0.69-1.38)	0.95 (0.48-1.88)	0.96 (0.52-1.76)	-0.05 (-0.75-0.64)
Null	1.03 (0.57-1.86)	1.03 (0.63-1.69)	0.96 (0.60-1.54)	0.96 (0.64-1.45)			
GSTP1 I105V rs947894	Studies included: IARC and Kyushu						
AA	1.00 (Reference)	1.00 (Reference)	1.04 (0.60-1.82)	1.01 (0.65-1.57)	0.91 (0.42-1.97)	0.93 (0.47-1.81)	-0.11 (-0.97-0.76)
AG + GG	1.14 (0.59-2.21)	1.09 (0.65-1.83)	1.08 (0.62-1.88)	1.04 (0.67-1.62)			
ATM C77T rs664677	Studies included: IARC and Seoul						
TT	1.00 (Reference)	1.00 (Reference)	0.89 (0.46-1.70)	0.98 (0.60-1.62)	1.53 (0.72-3.25)	1.39 (0.72-2.68)	0.34 (-0.21-0.90)
TC + CC	0.65 (0.35-1.20)	0.74 (0.46-1.19)	0.88 (0.49-1.56)	0.97 (0.63-1.51)			

Table 3-13. Joint associations of polymorphisms of DNA repair, carcinogen metabolism, and cell cycle control genes and exposure to ETS on lung cancer in never smokers

Genetic Variant dbSNP no.	Unexposed to ETS		Exposed to ETS		Multiplicative Interaction		Additive Interaction
	OR[a] (95% CI)	Bayesian Posterior OR[a] (95% CI)	OR[a] (95% CI)	Bayesian Posterior OR[a] (95% CI)	ROR[a] (95% CI)	Bayesian Posterior ROR[a] (95% CI)	RERI[a] (95% CI)
Cell cycle pathway							
TP53 R72P rs1042522	Studies included: IARC, Harvard, and UCLA						
GG	1.00 (Reference)	1.00 (Reference)	0.64 (0.40-1.02)	0.72 (0.49-1.08)	1.88 (0.99-3.55)	1.68 (0.95-2.99)	0.50 (0.09-0.91)
GC + CC	0.68 (0.40-1.17)	0.78 (0.50-1.23)	0.82 (0.53-1.29)	0.91 (0.62-1.34)			

ETS, environmental tobacco smoke; OR, odds ratio; CI, confidence interval; ROR, ratio of odds ratios; RERI, relative excess risk due to interaction
[a]Adjusted for age, sex, race/ethnicity, and study.

Table 3-14. Distribution of characteristics of lung cancer cases and controls in the Jiangsu and Taiyuan Studies

	Jiangsu Study			Taiyuan Study		
	Cases, N (%)	**Controls, N (%)**	**P[a]**	**Cases, N (%)**	**Controls, N (%)**	**P[a]**
Total	205	989		177	282	
Sex			<0.001			<0.001
Male	58 (28.3)	524 (53.0)		15 (8.5)	66 (23.4)	
Female	147 (71.7)	465 (47.0)		162 (91.5)	216 (76.6)	
Age (years)			0.336			0.788
<50	48 (23.4)	190 (19.2)		64 (36.2)	103 (36.5)	
50-59	50 (24.4)	214 (21.6)		61 (34.5)	86 (30.5)	
60-69	47 (22.9)	289 (29.2)		38 (21.5)	66 (23.4)	
70-79	48 (23.4)	233 (23.6)		14 (7.9)	27 (9.6)	
≥80	12 (5.8)	63 (6.4)		0	0	
Mean (SD)	60.1 (13.2)	61.6 (12.5)		53.0 (11.9)	53.9 (11.7)	
Education			0.070			<0.001
No formal education	118 (57.6)	473 (47.8)		27 (15.2)	18 (6.4)	
Primary school	50 (24.4)	277 (28.0)		48 (27.1)	49 (17.4)	
Middle school	27 (13.2)	164 (16.6)		49 (27.7)	108 (38.3)	
High school or above	10 (4.9)	75 (7.6)		53 (29.9)	107 (37.9)	
Income 10 years ago (Yuan/year)			0.147			<0.001
<1,000	39 (19.0)	142 (14.4)		51 (28.8)	69 (24.5)	
1,000-1,999	69 (33.7)	297 (30.0)		24 (13.6)	41 (14.5)	
2,000-2,999	48 (23.4)	279 (28.2)		79 (44.6)	81 (28.7)	
≥3,000	49 (23.9)	271 (27.4)		23 (13.0)	91 (32.3)	

SD, standard deviation

[a]P-value for χ^2-tests comparing cases and controls.

Table 3-15. Associations of ETS exposure with lung cancer by study

	Jiangsu Study				Taiyuan Study			
	Cases, N	**Controls, N**	**Crude OR (95% CI)**	**Adjusted OR[a] (95% CI)**	**Cases, N**	**Controls, N**	**Crude OR (95% CI)**	**Adjusted OR[a] (95% CI)**
Exposed to ETS								
Never	87	578	1.00 (Reference)	1.00 (Reference)	42	90	1.00 (Reference)	1.00 (Reference)
Ever	118	411	1.91 (1.41-2.59)	1.46 (1.05-2.02)	135	192	1.51 (0.98-2.31)	1.65 (1.04-2.63)
ETS exposure location								
None	87	578	1.00 (Reference)	1.00 (Reference)	42	90	1.00 (Reference)	1.00 (Reference)
Home only	94	309	2.02 (1.46-2.79)	1.42 (0.99-2.02)	75	107	1.50 (0.94-2.40)	1.29 (0.77-2.16)
Work only	6	49	0.81 (0.34-1.96)	1.25 (0.50-3.10)	29	37	1.68 (0.91-3.09)	3.27 (1.60-6.68)
Both home and work	16	52	2.04 (1.18-3.74)	1.76 (0.93-3.33)	31	48	1.38 (0.77-2.47)	1.84 (0.97-3.50)
ETS exposure duration (years)								
Never	87	578	1.00 (Reference)	1.00 (Reference)	42	90	1.00 (Reference)	1.00 (Reference)
1-19	24	125	1.28 (0.78-2.08)	1.04 (0.61-1.77)	33	48	1.47 (0.83-2.62)	1.69 (0.89-3.20)
20-39	55	194	1.88 (1.29-2.74)	1.36 (0.90-2.05)	55	75	1.57 (0.95-2.60)	1.80 (1.04-3.14)
40 or longer	37	89	2.76 (1.77-4.31)	2.22 (1.35-3.65)	21	32	1.41 (0.73-2.72)	1.30 (0.63-2.67)
P for trend			*<0.001*	*0.003*			*0.136*	*0.146*
Exposure intensity								
None	87	578	1.00 (Reference)	1.00 (Reference)	42	90	1.00 (Reference)	1.00 (Reference)
Light	35	129	1.80 (1.16-2.79)	1.10 (0.68-1.78)	45	65	1.48 (0.87-2.51)	1.51 (0.85-2.68)
Medium	43	158	1.81 (1.20-2.71)	1.43 (0.92-2.22)	39	84	0.99 (0.59-1.69)	1.08 (0.61-1.93)
Heavy	39	121	2.14 (1.40-3.28)	1.97 (1.24-3.12)	39	17	4.92 (2.50-9.68)	7.00 (3.32-14.75)
P for trend			*<0.001*	*0.003*			*0.001*	*<0.001*

OR, odds ratio; CI, confidence interval

[a]Odds ratios are adjusted for age, sex, income 10 years ago, education, and county of residence (Jiangsu only).

Table 3-16. Associations between polymorphisms of miRNA and stem cell regulation genes and lung cancer in never smokers by ETS exposure status

	All			Unexposed to ETS			Exposed to ETS		
Gene dbSNP no.	**Ca/Co**	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**Ca/Co**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**	**Ca/Co**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**
AGO2 rs4961280									
CC	290/923	1.00 (Reference)	1.00 (Reference)	97/487	1.00 (Reference)	1.00 (Reference)	193/436	1.00 (Reference)	1.00 (Reference)
CA	64/225	1.04 (0.75-1.45)	1.04 (0.75-1.43)	25/116	1.22 (0.73-2.03)	1.17 (0.75-1.83)	39/109	0.94 (0.60-1.46)	0.95 (0.64-1.41)
AA	3/25	0.41 (0.11-1.45)	0.60 (0.24-1.51)	2/11	0.69 (0.13-3.62)	0.90 (0.39-2.05)	1/14	0.22 (0.03-1.83)	0.74 (0.30-1.81)
P_{trend}		*0.586*	*0.593*		*0.699*	*0.722*		*0.319*	*0.353*
CTNNB1 rs2953									
TT	195/675	1.00 (Reference)	1.00 (Reference)	65/339	1.00 (Reference)	1.00 (Reference)	130/336	1.00 (Reference)	1.00 (Reference)
TG	137/457	1.05 (0.80-1.37)	1.05 (0.80-1.36)	48/257	0.92 (0.60-1.42)	0.93 (0.63-1.38)	89/200	1.18 (0.83-1.68)	1.16 (0.83-1.61)
GG	37/78	1.73 (1.09-2.76)	1.64 (1.06-2.54)	12/46	1.51 (0.73-3.13)	1.31 (0.73-2.33)	25/32	1.97 (1.06-3.68)	1.63 (0.97-2.75)
P_{trend}		*0.076*	*0.078*		*0.594*	*0.611*		*0.044*	*0.051*
CXCL12 rs1804429									
TT	327/1057	1.00 (Reference)	1.00 (Reference)	113/557	1.00 (Reference)	1.00 (Reference)	214/500	1.00 (Reference)	1.00 (Reference)
TG	39/137	0.96 (0.64-1.45)	0.97 (0.65-1.43)	13/73	0.85 (0.44-1.66)	0.90 (0.52-1.55)	26/64	1.01 (0.60-1.72)	1.01 (0.64-1.61)
GG	0/7			0/3			0/4		
DDX20 rs197412									
TT	166/528	1.00 (Reference)	1.00 (Reference)	57/281	1.00 (Reference)	1.00 (Reference)	109/247	1.00 (Reference)	1.00 (Reference)
TC	145/538	0.91 (0.69-1.20)	0.92 (0.70-1.20)	51/276	0.93 (0.60-1.43)	0.94 (0.63-1.39)	94/262	0.93 (0.65-1.32)	0.94 (0.67-1.30)
CC	51/127	1.27 (0.85-1.91)	1.25 (0.85-1.84)	14/68	1.04 (0.53-2.05)	1.03 (0.59-1.78)	37/59	1.39 (0.83-2.33)	1.30 (0.82-2.04)
P_{trend}		*0.542*	*0.545*		*0.935*	*0.938*		*0.430*	*0.442*
DICER1 rs3742330									
AA	148/529	1.00 (Reference)	1.00 (Reference)	50/296	1.00 (Reference)	1.00 (Reference)	98/233	1.00 (Reference)	1.00 (Reference)
AG	163/518	1.07 (0.81-1.41)	1.07 (0.82-1.40)	54/261	1.23 (0.79-1.91)	1.18 (0.79-1.77)	109/257	0.96 (0.67-1.37)	0.97 (0.69-1.35)
GG	50/173	1.03 (0.69-1.54)	1.03 (0.70-1.51)	19/85	1.41 (0.76-2.61)	1.28 (0.76-2.15)	31/88	0.80 (0.48-1.35)	0.84 (0.53-1.33)
P_{trend}		*0.755*	*0.757*		*0.229*	*0.248*		*0.460*	*0.472*

Table 3-16. Associations between polymorphisms of miRNA and stem cell regulation genes and lung cancer in never smokers by ETS exposure status

	All			Unexposed to ETS			Exposed to ETS		
Gene dbSNP no.	**Ca/Co**	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**Ca/Co**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**	**Ca/Co**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**
DOCK4 rs3801790									
AA	142/439	1.00 (Reference)	1.00 (Reference)	45/222	1.00 (Reference)	1.00 (Reference)	97/217	1.00 (Reference)	1.00 (Reference)
AG	157/547	0.95 (0.72-1.26)	0.95 (0.72-1.26)	54/295	0.99 (0.62-1.56)	0.99 (0.65-1.49)	103/252	0.93 (0.65-1.34)	0.94 (0.67-1.32)
GG	58/201	1.02 (0.70-1.48)	1.02 (0.71-1.46)	23/107	1.32 (0.73-2.38)	1.23 (0.74-2.03)	35/94	0.84 (0.51-1.38)	0.87 (0.56-1.35)
P_{trend}		*0.974*	*0.974*		*0.451*	*0.468*		*0.489*	*0.500*
E2F2 rs2075993									
GG	138/434	1.00 (Reference)	1.00 (Reference)	48/221	1.00 (Reference)	1.00 (Reference)	90/213	1.00 (Reference)	1.00 (Reference)
GA	154/523	0.87 (0.66-1.16)	0.88 (0.67-1.16)	51/275	0.82 (0.52-1.30)	0.85 (0.56-1.28)	103/248	0.88 (0.61-1.28)	0.90 (0.64-1.26)
AA	59/201	0.80 (0.55-1.16)	0.81 (0.56-1.16)	21/108	0.76 (0.42-1.38)	0.82 (0.49-1.35)	38/93	0.79 (0.48-1.29)	0.83 (0.54-1.28)
P_{trend}		*0.202*	*0.205*		*0.313*	*0.332*		*0.326*	*0.339*
GEMIN4 rs2740348									
GG	277/951	1.00 (Reference)	1.00 (Reference)	97/508	1.00 (Reference)	1.00 (Reference)	180/443	1.00 (Reference)	1.00 (Reference)
GC	73/191	1.34 (0.96-1.86)	1.32 (0.96-1.81)	25/93	1.54 (0.91-2.60)	1.40 (0.88-2.22)	48/98	1.23 (0.81-1.87)	1.19 (0.81-1.75)
CC	5/29	0.51 (0.18-1.39)	0.64 (0.28-1.42)	2/15	0.75 (0.15-3.67)	0.92 (0.40-2.07)	3/14	0.42 (0.11-1.58)	0.72 (0.33-1.58)
P_{trend}		*0.569*	*0.575*		*0.296*	*0.335*		*0.991*	*0.991*
GEMIN4 rs7813									
TT	172/611	1.00 (Reference)	1.00 (Reference)	51/338	1.00 (Reference)	1.00 (Reference)	121/273	1.00 (Reference)	1.00 (Reference)
CT	149/441	1.29 (0.98-1.70)	1.28 (0.98-1.67)	52/213	2.00 (1.27-3.14)	1.77 (1.18-2.67)	97/228	0.96 (0.68-1.37)	0.97 (0.69-1.34)
CC	35/114	1.05 (0.68-1.65)	1.05 (0.69-1.60)	19/63	2.07 (1.10-3.91)	1.68 (0.99-2.85)	16/51	0.58 (0.31-1.10)	0.68 (0.40-1.16)
P_{trend}		*0.272*	*0.276*		*0.002*	*0.004*		*0.192*	*0.206*
IL15 rs10519613									
CC	125/413	1.00 (Reference)	1.00 (Reference)	45/227	1.00 (Reference)	1.00 (Reference)	80/186	1.00 (Reference)	1.00 (Reference)
CA	168/560	0.92 (0.69-1.23)	0.93 (0.70-1.23)	55/293	1.00 (0.63-1.58)	1.00 (0.66-1.51)	113/267	0.88 (0.61-1.29)	0.90 (0.63-1.27)
AA	68/221	0.87 (0.60-1.26)	0.88 (0.62-1.25)	24/107	1.04 (0.58-1.86)	1.03 (0.63-1.69)	44/114	0.76 (0.47-1.22)	0.80 (0.52-1.22)
P_{trend}		*0.440*	*0.444*		*0.899*	*0.902*		*0.252*	*0.265*

Table 3-16. Associations between polymorphisms of miRNA and stem cell regulation genes and lung cancer in never smokers by ETS exposure status

	All			Unexposed to ETS			Exposed to ETS		
Gene dbSNP no.	**Ca/Co**	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**Ca/Co**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**	**Ca/Co**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**
IL6R rs4072391									
CC	315/997	1.00 (Reference)	1.00 (Reference)	112/529	1.00 (Reference)	1.00 (Reference)	203/468	1.00 (Reference)	1.00 (Reference)
CT	46/192	0.82 (0.56-1.19)	0.83 (0.58-1.19)	12/98	0.57 (0.30-1.11)	0.68 (0.39-1.17)	34/94	1.03 (0.65-1.64)	1.02 (0.67-1.56)
TT	4/17	1.24 (0.39-3.97)	1.14 (0.48-2.72)	1/9	0.93 (0.11-7.74)	0.98 (0.41-2.34)	3/8	1.52 (0.36-6.50)	1.15 (0.52-2.56)
P_{trend}		*0.466*	*0.476*		*0.141*	*0.202*		*0.708*	*0.728*
KRAS rs9266									
CC	236/786	1.00 (Reference)	1.00 (Reference)	76/410	1.00 (Reference)	1.00 (Reference)	160/376	1.00 (Reference)	1.00 (Reference)
CT	121/373	1.00 (0.76-1.32)	1.00 (0.77-1.31)	43/195	1.06 (0.68-1.63)	1.05 (0.70-1.56)	78/178	0.99 (0.69-1.41)	0.99 (0.71-1.38)
TT	13/50	0.79 (0.40-1.55)	0.82 (0.45-1.50)	6/29	0.88 (0.33-2.34)	0.94 (0.47-1.85)	7/21	0.73 (0.29-1.86)	0.84 (0.43-1.65)
P_{trend}		*0.689*	*0.692*		*0.990*	*0.991*		*0.672*	*0.684*
miR-196a2 rs11614913									
TT	110/400	1.00 (Reference)	1.00 (Reference)	34/225	1.00 (Reference)	1.00 (Reference)	76/175	1.00 (Reference)	1.00 (Reference)
CT	150/535	1.02 (0.75-1.37)	1.01 (0.76-1.36)	56/261	1.41 (0.87-2.30)	1.32 (0.86-2.04)	94/274	0.83 (0.56-1.22)	0.85 (0.59-1.22)
CC	101/243	1.35 (0.96-1.90)	1.32 (0.95-1.84)	34/133	1.48 (0.85-2.57)	1.35 (0.83-2.17)	67/110	1.26 (0.80-1.97)	1.21 (0.81-1.81)
P_{trend}		*0.103*	*0.106*		*0.150*	*0.164*		*0.390*	*0.401*
miR-26a1 rs7372209									
CC	171/597	1.00 (Reference)	1.00 (Reference)	62/321	1.00 (Reference)	1.00 (Reference)	109/276	1.00 (Reference)	1.00 (Reference)
CT	151/513	1.02 (0.78-1.34)	1.02 (0.79-1.33)	52/259	1.09 (0.71-1.67)	1.07 (0.73-1.58)	99/254	0.99 (0.69-1.40)	0.99 (0.71-1.37)
TT	39/103	1.43 (0.92-2.22)	1.39 (0.91-2.10)	11/56	0.95 (0.45-2.00)	0.97 (0.54-1.74)	28/47	1.94 (1.09-3.44)	1.64 (1.00-2.69)
P_{trend}		*0.217*	*0.221*		*0.917*	*0.921*		*0.116*	*0.128*
miR-27 rs895819									
TT	207/698	1.00 (Reference)	1.00 (Reference)	70/363	1.00 (Reference)	1.00 (Reference)	137/335	1.00 (Reference)	1.00 (Reference)
TC	136/399	1.11 (0.85-1.46)	1.11 (0.85-1.44)	49/204	1.27 (0.83-1.95)	1.22 (0.83-1.81)	87/195	1.00 (0.71-1.43)	1.00 (0.72-1.40)
CC	26/97	0.94 (0.57-1.54)	0.94 (0.59-1.51)	8/58	0.73 (0.32-1.66)	0.83 (0.44-1.54)	18/39	1.06 (0.55-2.04)	1.04 (0.61-1.79)
P_{trend}		*0.786*	*0.788*		*0.932*	*0.935*		*0.889*	*0.892*

Table 3-16. Associations between polymorphisms of miRNA and stem cell regulation genes and lung cancer in never smokers by ETS exposure status

	All			Unexposed to ETS			Exposed to ETS		
Gene dbSNP no.	**Ca/Co**	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**Ca/Co**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**	**Ca/Co**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**
miR-300 rs12894467									
TT	215/747	1.00 (Reference)	1.00 (Reference)	66/395	1.00 (Reference)	1.00 (Reference)	149/352	1.00 (Reference)	1.00 (Reference)
CT	125/363	1.22 (0.92-1.61)	1.21 (0.92-1.59)	50/181	1.66 (1.07-2.57)	1.52 (1.02-2.27)	75/182	1.01 (0.71-1.46)	1.01 (0.72-1.42)
CC	14/69	0.66 (0.35-1.24)	0.71 (0.40-1.25)	6/40	0.77 (0.30-2.00)	0.87 (0.45-1.71)	8/29	0.59 (0.25-1.40)	0.74 (0.39-1.40)
P_{trend}		*0.905*	*0.906*		*0.283*	*0.307*		*0.486*	*0.503*
pre-miR-146a rs2910164									
CC	118/434	1.00 (Reference)	1.00 (Reference)	34/246	1.00 (Reference)	1.00 (Reference)	84/188	1.00 (Reference)	1.00 (Reference)
GC	172/552	1.15 (0.86-1.53)	1.14 (0.86-1.51)	67/276	1.88 (1.18-3.02)	1.67 (1.10-2.56)	105/276	0.81 (0.56-1.18)	0.83 (0.59-1.18)
GG	71/222	1.19 (0.83-1.72)	1.18 (0.83-1.68)	23/114	1.70 (0.93-3.12)	1.47 (0.88-2.46)	48/108	0.94 (0.59-1.51)	0.95 (0.63-1.45)
P_{trend}		*0.295*	*0.298*		*0.033*	*0.040*		*0.646*	*0.655*
RAN rs14035									
CC	260/766	1.00 (Reference)	1.00 (Reference)	84/408	1.00 (Reference)	1.00 (Reference)	176/358	1.00 (Reference)	1.00 (Reference)
CT	83/333	0.74 (0.55-1.00)	0.75 (0.56-1.01)	32/170	0.92 (0.58-1.48)	0.94 (0.61-1.43)	51/163	0.62 (0.42-0.93)	0.67 (0.46-0.96)
TT	11/54	0.78 (0.38-1.61)	0.82 (0.44-1.55)	6/27	1.72 (0.66-4.52)	1.33 (0.67-2.62)	5/27	0.37 (0.13-1.06)	0.62 (0.30-1.28)
P_{trend}		*0.067*	*0.070*		*0.675*	*0.693*		*0.004*	*0.007*
RBL2 *rs3929*									
GG	258/832	1.00 (Reference)	1.00 (Reference)	92/437	1.00 (Reference)	1.00 (Reference)	166/395	1.00 (Reference)	1.00 (Reference)
CG	98/351	0.93 (0.70-1.24)	0.94 (0.71-1.24)	30/187	0.86 (0.54-1.38)	0.89 (0.58-1.35)	68/164	0.95 (0.66-1.37)	0.95 (0.68-1.34)
CC	14/39	1.30 (0.66-2.57)	1.24 (0.68-2.26)	5/17	1.26 (0.43-3.70)	1.12 (0.55-2.28)	9/22	1.48 (0.60-3.61)	1.24 (0.65-2.39)
P_{trend}		*0.943*	*0.943*		*0.822*	*0.833*		*0.802*	*0.811*
THBS1 *rs2292305*									
TT	162/533	1.00 (Reference)	1.00 (Reference)	57/260	1.00 (Reference)	1.00 (Reference)	105/273	1.00 (Reference)	1.00 (Reference)
CT	160/509	1.02 (0.78-1.34)	1.02 (0.78-1.33)	56/284	0.88 (0.57-1.36)	0.90 (0.61-1.33)	104/225	1.10 (0.77-1.56)	1.08 (0.78-1.51)
CC	37/140	0.86 (0.56-1.32)	0.87 (0.58-1.31)	12/80	0.65 (0.33-1.32)	0.75 (0.43-1.33)	25/60	1.02 (0.58-1.77)	1.01 (0.63-1.64)
P_{trend}		*0.641*	*0.644*		*0.244*	*0.264*		*0.775*	*0.781*

Table 3-16. Associations between polymorphisms of miRNA and stem cell regulation genes and lung cancer in never smokers by ETS exposure status

	All			Unexposed to ETS			Exposed to ETS		
Gene dbSNP no.	**Ca/Co**	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**Ca/Co**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**	**Ca/Co**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**
TP53INP1 rs7760									
TT	283/894	1.00 (Reference)	1.00 (Reference)	94/471	1.00 (Reference)	1.00 (Reference)	189/423	1.00 (Reference)	1.00 (Reference)
TG	68/264	0.76 (0.55-1.05)	0.77 (0.56-1.05)	27/136	0.92 (0.56-1.51)	0.94 (0.60-1.46)	41/128	0.69 (0.45-1.06)	0.73 (0.50-1.08)
GG	10/36	0.82 (0.38-1.79)	0.86 (0.44-1.68)	2/20	0.61 (0.13-2.76)	0.85 (0.38-1.91)	8/16	0.98 (0.38-2.54)	0.99 (0.51-1.94)
P_{trend}		*0.122*	*0.127*		*0.532*	*0.563*		*0.200*	*0.223*
TP53INP1 rs896849									
TT	283/887	1.00 (Reference)	1.00 (Reference)	94/466	1.00 (Reference)	1.00 (Reference)	189/421	1.00 (Reference)	1.00 (Reference)
TC	69/270	0.73 (0.53-1.01)	0.74 (0.54-1.01)	27/142	0.81 (0.49-1.34)	0.85 (0.54-1.32)	42/128	0.70 (0.46-1.07)	0.74 (0.50-1.09)
CC	10/45	0.71 (0.33-1.52)	0.77 (0.40-1.48)	3/23	0.88 (0.25-3.08)	0.95 (0.44-2.02)	7/22	0.71 (0.27-1.84)	0.83 (0.42-1.64)
P_{trend}		*0.050*	*0.054*		*0.457*	*0.490*		*0.099*	*0.117*
WNT2B rs2273368									
CC	110/360	1.00 (Reference)	1.00 (Reference)	42/170	1.00 (Reference)	1.00 (Reference)	68/190	1.00 (Reference)	1.00 (Reference)
CT	176/571	1.05 (0.78-1.41)	1.05 (0.79-1.40)	56/313	0.72 (0.45-1.16)	0.77 (0.50-1.17)	120/258	1.37 (0.94-2.02)	1.32 (0.92-1.88)
TT	78/259	1.11 (0.78-1.60)	1.11 (0.78-1.57)	27/141	0.80 (0.45-1.41)	0.84 (0.52-1.38)	51/118	1.42 (0.89-2.27)	1.33 (0.87-2.03)
P_{trend}		*0.555*	*0.558*		*0.368*	*0.387*		*0.111*	*0.121*
WWOX rs12828									
GG	133/500	1.00 (Reference)	1.00 (Reference)	52/263	1.00 (Reference)	1.00 (Reference)	81/237	1.00 (Reference)	1.00 (Reference)
AG	162/514	1.04 (0.79-1.38)	1.04 (0.79-1.37)	59/266	0.99 (0.64-1.53)	0.99 (0.67-1.47)	103/248	1.10 (0.76-1.60)	1.09 (0.77-1.54)
AA	54/173	1.03 (0.70-1.52)	1.03 (0.71-1.50)	11/92	0.57 (0.28-1.18)	0.69 (0.39-1.24)	43/81	1.39 (0.85-2.27)	1.30 (0.84-2.01)
P_{trend}		*0.826*	*0.827*		*0.230*	*0.251*		*0.213*	*0.225*
XPO5 rs11077									
AA	313/1,040	1.00 (Reference)	1.00 (Reference)	105/561	1.00 (Reference)	1.00 (Reference)	208/479	1.00 (Reference)	1.00 (Reference)
AC	49/151	0.84 (0.58-1.22)	0.85 (0.59-1.22)	20/68	1.27 (0.71-2.26)	1.19 (0.73-1.95)	29/83	0.65 (0.40-1.06)	0.71 (0.46-1.09)
CC	2/15	0.39 (0.08-1.80)	0.63 (0.23-1.74)	2/7	1.20 (0.22-6.47)	1.05 (0.46-2.41)	0/8		
P_{trend}		*0.167*	*0.177*		*0.445*	*0.49*			

Table 3-16. Associations between polymorphisms of miRNA and stem cell regulation genes and lung cancer in never smokers by ETS exposure status

	All			Unexposed to ETS			Exposed to ETS		
Gene dbSNP no.	**Ca/Co**	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**Ca/Co**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**	**Ca/Co**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**
AXIN1 rs1981492									
GG	165/603	1.00 (Reference)	1.00 (Reference)	51/346	1.00 (Reference)	1.00 (Reference)	114/257	1.00 (Reference)	1.00 (Reference)
AG	154/466	1.10 (0.84-1.45)	1.10 (0.84-1.43)	59/225	1.68 (1.09-2.61)	1.55 (1.04-2.30)	95/241	0.88 (0.61-1.25)	0.89 (0.64-1.24)
AA	37/118	0.95 (0.61-1.47)	0.95 (0.63-1.45)	13/56	1.62 (0.79-3.32)	1.37 (0.77-2.44)	24/62	0.70 (0.40-1.22)	0.76 (0.47-1.23)
P_{trend}		*0.866*	*0.867*		*0.032*	*0.040*		*0.191*	*0.204*
AXIN2 rs2240308									
GG	169/562	1.00 (Reference)	1.00 (Reference)	65/304	1.00 (Reference)	1.00 (Reference)	104/258	1.00 (Reference)	1.00 (Reference)
AG	142/436	1.01 (0.76-1.35)	1.01 (0.77-1.34)	47/215	1.01 (0.64-1.58)	1.00 (0.67-1.51)	95/221	1.03 (0.72-1.50)	1.03 (0.73-1.45)
AA	47/124	1.37 (0.91-2.08)	1.34 (0.90-1.99)	14/66	1.04 (0.53-2.03)	1.02 (0.59-1.78)	33/58	1.66 (0.96-2.87)	1.48 (0.92-2.37)
P_{trend}		*0.235*	*0.239*		*0.930*	*0.932*		*0.142*	*0.154*
CTBP2 rs3740535									
GG	210/667	1.00 (Reference)	1.00 (Reference)	70/352	1.00 (Reference)	1.00 (Reference)	140/315	1.00 (Reference)	1.00 (Reference)
AG	124/453	0.81 (0.62-1.06)	0.82 (0.62-1.07)	48/237	0.95 (0.62-1.45)	0.95 (0.65-1.41)	76/216	0.72 (0.50-1.03)	0.75 (0.54-1.05)
AA	36/87	1.13 (0.72-1.77)	1.12 (0.73-1.71)	9/50	0.76 (0.34-1.68)	0.84 (0.46-1.55)	27/37	1.54 (0.86-2.76)	1.38 (0.84-2.27)
P_{trend}		*0.642*	*0.645*		*0.533*	*0.552*		*0.952*	*0.953*
DEC1 rs2269700									
TT	237/806	1.00 (Reference)	1.00 (Reference)	80/415	1.00 (Reference)	1.00 (Reference)	157/391	1.00 (Reference)	1.00 (Reference)
CT	111/351	0.99 (0.75-1.31)	0.99 (0.75-1.30)	39/189	1.00 (0.64-1.56)	1.00 (0.67-1.50)	72/162	0.97 (0.67-1.39)	0.97 (0.69-1.36)
CC	16/54	1.12 (0.60-2.10)	1.10 (0.63-1.94)	7/30	1.15 (0.45-2.91)	1.08 (0.55-2.10)	9/24	1.10 (0.47-2.58)	1.06 (0.56-1.99)
P_{trend}		*0.865*	*0.866*		*0.850*	*0.858*		*0.988*	*0.989*
DLL1 rs1033583									
AA	212/642	1.00 (Reference)	1.00 (Reference)	70/331	1.00 (Reference)	1.00 (Reference)	142/311	1.00 (Reference)	1.00 (Reference)
AC	130/376	0.99 (0.75-1.31)	0.99 (0.76-1.30)	50/205	1.06 (0.69-1.63)	1.05 (0.71-1.55)	80/171	0.94 (0.66-1.35)	0.95 (0.68-1.33)
CC	17/66	0.66 (0.36-1.19)	0.70 (0.41-1.20)	3/35	0.30 (0.09-1.05)	0.62 (0.29-1.35)	14/31	0.91 (0.44-1.85)	0.94 (0.53-1.66)
P_{trend}		*0.351*	*0.356*		*0.281*	*0.307*		*0.700*	*0.710*

Table 3-16. Associations between polymorphisms of miRNA and stem cell regulation genes and lung cancer in never smokers by ETS exposure status

	All			Unexposed to ETS			Exposed to ETS		
Gene dbSNP no.	**Ca/Co**	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**Ca/Co**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**	**Ca/Co**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**
DLL1 rs1421									
AA	243/815	1.00 (Reference)	1.00 (Reference)	79/428	1.00 (Reference)	1.00 (Reference)	164/387	1.00 (Reference)	1.00 (Reference)
AG	99/330	0.99 (0.74-1.31)	0.99 (0.74-1.31)	39/175	1.15 (0.73-1.80)	1.12 (0.74-1.68)	60/155	0.93 (0.64-1.36)	0.94 (0.66-1.34)
GG	18/50	1.43 (0.77-2.66)	1.35 (0.77-2.37)	6/27	1.49 (0.56-3.91)	1.23 (0.62-2.43)	12/23	1.41 (0.63-3.17)	1.23 (0.66-2.28)
P_{trend}		*0.535*	*0.540*		*0.365*	*0.393*		*0.798*	*0.805*
DVL2 rs222851									
AA	134/497	1.00 (Reference)	1.00 (Reference)	45/267	1.00 (Reference)	1.00 (Reference)	89/230	1.00 (Reference)	1.00 (Reference)
AG	164/528	1.09 (0.83-1.45)	1.09 (0.83-1.43)	52/280	1.06 (0.67-1.68)	1.05 (0.70-1.59)	112/248	1.09 (0.76-1.57)	1.08 (0.77-1.51)
GG	52/151	1.29 (0.86-1.92)	1.26 (0.86-1.85)	25/76	1.84 (1.02-3.31)	1.57 (0.95-2.59)	27/75	0.96 (0.55-1.66)	0.97 (0.60-1.56)
P_{trend}		*0.226*	*0.230*		*0.081*	*0.094*		*0.933*	*0.935*
EPCAM rs1126497									
CC	225/824	1.00 (Reference)	1.00 (Reference)	76/435	1.00 (Reference)	1.00 (Reference)	149/389	1.00 (Reference)	1.00 (Reference)
CT	128/325	1.40 (1.06-1.84)	1.38 (1.05-1.80)	45/167	1.39 (0.90-2.16)	1.32 (0.89-1.97)	83/158	1.36 (0.95-1.95)	1.31 (0.94-1.84)
TT	10/70	0.55 (0.27-1.13)	0.62 (0.33-1.17)	3/41	0.42 (0.12-1.45)	0.71 (0.33-1.51)	7/29	0.58 (0.24-1.44)	0.74 (0.38-1.43)
P_{trend}		*0.503*	*0.508*		*0.920*	*0.924*		*0.618*	*0.631*
FZD3 rs2228224									
GG	202/660	1.00 (Reference)	1.00 (Reference)	65/347	1.00 (Reference)	1.00 (Reference)	137/313	1.00 (Reference)	1.00 (Reference)
AG	132/423	0.98 (0.75-1.29)	0.98 (0.75-1.28)	53/222	1.25 (0.82-1.91)	1.21 (0.82-1.78)	79/201	0.87 (0.61-1.26)	0.89 (0.63-1.25)
AA	26/104	0.82 (0.50-1.34)	0.84 (0.53-1.33)	6/54	0.67 (0.27-1.69)	0.81 (0.41-1.56)	20/50	0.92 (0.51-1.67)	0.94 (0.57-1.56)
P_{trend}		*0.535*	*0.539*		*0.939*	*0.942*		*0.554*	*0.566*
FZD3 rs2241802									
GG	122/379	1.00 (Reference)	1.00 (Reference)	39/194	1.00 (Reference)	1.00 (Reference)	83/185	1.00 (Reference)	1.00 (Reference)
AG	173/567	1.03 (0.77-1.37)	1.02 (0.77-1.36)	65/291	1.20 (0.75-1.91)	1.16 (0.76-1.76)	108/276	0.96 (0.66-1.40)	0.97 (0.68-1.37)
AA	67/217	1.02 (0.70-1.48)	1.02 (0.71-1.45)	21/123	0.80 (0.43-1.48)	0.85 (0.51-1.43)	46/94	1.20 (0.74-1.96)	1.16 (0.75-1.79)
P_{trend}		*0.908*	*0.909*		*0.637*	*0.649*		*0.549*	*0.559*

Table 3-16. Associations between polymorphisms of miRNA and stem cell regulation genes and lung cancer in never smokers by ETS exposure status

	All			Unexposed to ETS			Exposed to ETS		
Gene dbSNP no.	**Ca/Co**	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**Ca/Co**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**	**Ca/Co**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**
HES2 rs11364									
GG	254/737	1.00 (Reference)	1.00 (Reference)	85/381	1.00 (Reference)	1.00 (Reference)	169/356	1.00 (Reference)	1.00 (Reference)
AG	90/278	0.95 (0.70-1.28)	0.95 (0.71-1.27)	35/151	0.95 (0.60-1.50)	0.96 (0.63-1.45)	55/127	0.96 (0.65-1.43)	0.97 (0.67-1.40)
AA	14/35	1.29 (0.66-2.53)	1.23 (0.67-2.24)	3/16	0.85 (0.23-3.15)	0.94 (0.43-2.03)	11/19	1.59 (0.70-3.58)	1.32 (0.71-2.45)
P_{trend}		*0.863*	*0.865*		*0.753*	*0.769*		*0.566*	*0.582*
HES2 rs8708									
AA	239/799	1.00 (Reference)	1.00 (Reference)	81/422	1.00 (Reference)	1.00 (Reference)	158/377	1.00 (Reference)	1.00 (Reference)
AG	110/344	1.06 (0.80-1.40)	1.06 (0.80-1.39)	41/188	1.27 (0.82-1.97)	1.22 (0.82-1.82)	69/156	0.93 (0.64-1.35)	0.94 (0.67-1.32)
GG	14/48	1.01 (0.52-1.97)	1.01 (0.56-1.83)	3/25	0.74 (0.21-2.63)	0.89 (0.41-1.90)	11/23	1.19 (0.52-2.70)	1.11 (0.60-2.06)
P_{trend}		*0.754*	*0.756*		*0.574*	*0.596*		*0.979*	*0.980*
HEY1 rs1046472									
CC	241/730	1.00 (Reference)	1.00 (Reference)	83/389	1.00 (Reference)	1.00 (Reference)	158/341	1.00 (Reference)	1.00 (Reference)
AC	113/418	0.75 (0.57-0.99)	0.76 (0.58-0.99)	39/217	0.78 (0.50-1.21)	0.81 (0.54-1.21)	74/201	0.73 (0.51-1.04)	0.76 (0.54-1.06)
AA	13/54	0.63 (0.33-1.23)	0.69 (0.38-1.25)	3/28	0.45 (0.13-1.55)	0.72 (0.34-1.55)	10/26	0.71 (0.31-1.64)	0.82 (0.44-1.53)
P_{trend}		*0.022*	*0.024*		*0.113*	*0.137*		*0.087*	*0.100*
HEY2 rs3734637									
AA	235/684	1.00 (Reference)	1.00 (Reference)	81/365	1.00 (Reference)	1.00 (Reference)	154/319	1.00 (Reference)	1.00 (Reference)
AC	106/428	0.68 (0.52-0.90)	0.69 (0.53-0.91)	40/226	0.75 (0.48-1.16)	0.79 (0.53-1.17)	66/202	0.62 (0.43-0.89)	0.66 (0.47-0.92)
CC	21/88	0.71 (0.41-1.20)	0.74 (0.45-1.21)	5/48	0.51 (0.19-1.38)	0.71 (0.36-1.42)	16/40	0.82 (0.42-1.57)	0.87 (0.51-1.49)
P_{trend}		*0.011*	*0.012*		*0.085*	*0.103*		*0.049*	*0.057*
NOTCH4 rs520692									
AA	265/887	1.00 (Reference)	1.00 (Reference)	92/461	1.00 (Reference)	1.00 (Reference)	173/426	1.00 (Reference)	1.00 (Reference)
AG	89/284	0.96 (0.71-1.30)	0.96 (0.72-1.29)	30/155	0.86 (0.53-1.39)	0.89 (0.58-1.36)	59/129	1.10 (0.74-1.62)	1.08 (0.75-1.56)
GG	7/30	0.80 (0.33-1.94)	0.85 (0.41-1.77)	2/16	0.57 (0.12-2.65)	0.84 (0.37-1.89)	5/14	1.01 (0.33-3.06)	1.00 (0.49-2.07)
P_{trend}		*0.640*	*0.645*		*0.382*	*0.418*		*0.705*	*0.718*

Table 3-16. Associations between polymorphisms of miRNA and stem cell regulation genes and lung cancer in never smokers by ETS exposure status

	All			Unexposed to ETS			Exposed to ETS		
Gene dbSNP no.	**Ca/Co**	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**Ca/Co**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**	**Ca/Co**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**
NOTCH4 rs915894									
CC	94/350	1.00 (Reference)	1.00 (Reference)	36/187	1.00 (Reference)	1.00 (Reference)	58/163	1.00 (Reference)	1.00 (Reference)
AC	190/556	1.32 (0.98-1.79)	1.30 (0.97-1.75)	68/279	1.40 (0.87-2.25)	1.31 (0.86-2.01)	122/277	1.28 (0.86-1.91)	1.24 (0.86-1.79)
AA	70/281	0.98 (0.68-1.43)	0.98 (0.69-1.41)	22/156	0.79 (0.43-1.44)	0.84 (0.50-1.40)	48/125	1.11 (0.68-1.80)	1.09 (0.70-1.68)
P_{trend}		*0.912*	*0.913*		*0.581*	*0.595*		*0.614*	*0.624*
OCT4 rs13409									
CC	117/462	1.00 (Reference)	1.00 (Reference)	34/232	1.00 (Reference)	1.00 (Reference)	83/230	1.00 (Reference)	1.00 (Reference)
CT	168/523	1.38 (1.03-1.84)	1.36 (1.03-1.80)	60/286	1.53 (0.95-2.48)	1.41 (0.92-2.17)	108/237	1.28 (0.88-1.85)	1.24 (0.88-1.75)
TT	73/204	1.45 (1.01-2.09)	1.41 (1.00-2.01)	31/104	2.13 (1.20-3.80)	1.76 (1.07-2.89)	42/100	1.10 (0.68-1.77)	1.08 (0.70-1.65)
P_{trend}		*0.024*	*0.025*		*0.009*	*0.011*		*0.496*	*0.506*
OCT4 rs3130932									
TT	177/550	1.00 (Reference)	1.00 (Reference)	62/281	1.00 (Reference)	1.00 (Reference)	115/269	1.00 (Reference)	1.00 (Reference)
GT	145/505	0.97 (0.74-1.28)	0.97 (0.74-1.27)	49/278	0.83 (0.54-1.29)	0.86 (0.58-1.27)	96/227	1.09 (0.76-1.55)	1.08 (0.77-1.50)
GG	37/149	0.76 (0.49-1.17)	0.78 (0.52-1.17)	11/74	0.73 (0.35-1.52)	0.82 (0.46-1.46)	26/75	0.79 (0.46-1.35)	0.83 (0.52-1.33)
P_{trend}		*0.293*	*0.297*		*0.303*	*0.326*		*0.643*	*0.651*
REX1 rs6815391									
TT	138/511	1.00 (Reference)	1.00 (Reference)	44/279	1.00 (Reference)	1.00 (Reference)	94/232	1.00 (Reference)	1.00 (Reference)
CT	158/493	1.18 (0.89-1.56)	1.17 (0.89-1.54)	60/251	1.47 (0.94-2.30)	1.37 (0.91-2.06)	98/242	1.05 (0.73-1.52)	1.05 (0.74-1.47)
CC	59/168	1.16 (0.79-1.70)	1.15 (0.80-1.65)	19/82	1.34 (0.71-2.50)	1.23 (0.73-2.08)	40/86	1.09 (0.67-1.76)	1.07 (0.70-1.64)
P_{trend}		*0.309*	*0.313*		*0.187*	*0.204*		*0.71*	*0.717*
WNT2 rs3729629									
GG	183/521	1.00 (Reference)	1.00 (Reference)	58/261	1.00 (Reference)	1.00 (Reference)	125/260	1.00 (Reference)	1.00 (Reference)
CG	155/550	0.83 (0.63-1.08)	0.83 (0.64-1.08)	59/303	0.82 (0.54-1.25)	0.85 (0.58-1.25)	96/247	0.83 (0.58-1.17)	0.84 (0.61-1.17)
CC	32/135	0.63 (0.40-0.99)	0.66 (0.43-1.01)	9/69	0.61 (0.28-1.33)	0.73 (0.40-1.34)	23/66	0.64 (0.36-1.13)	0.71 (0.44-1.16)
P_{trend}		*0.030*	*0.032*		*0.168*	*0.188*		*0.092*	*0.101*

Table 3-16. Associations between polymorphisms of miRNA and stem cell regulation genes and lung cancer in never smokers by ETS exposure status

	All			Unexposed to ETS			Exposed to ETS		
Gene dbSNP no.	**Ca/Co**	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**Ca/Co**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**	**Ca/Co**	**OR[b] (95% CI)**	**Bayesian Posterior OR[b] (95% CI)**
WNT2 rs4730775									
CC	166/427	1.00 (Reference)	1.00 (Reference)	74/341	1.00 (Reference)	1.00 (Reference)	136/323	1.00 (Reference)	1.00 (Reference)
CT	204/540	0.86 (0.65-1.13)	0.86 (0.66-1.13)	40/245	0.73 (0.47-1.13)	0.77 (0.51-1.14)	83/197	0.98 (0.68-1.39)	0.98 (0.70-1.36)
TT	84/203	1.11 (0.68-1.82)	1.10 (0.69-1.75)	11/40	1.43 (0.67-3.05)	1.26 (0.69-2.27)	17/43	0.93 (0.49-1.78)	0.95 (0.56-1.63)
P_{trend}		*0.706*	*0.709*		*0.798*	*0.807*		*0.820*	*0.826*
WNT8A rs4835761									
AA	135/423	1.00 (Reference)	1.00 (Reference)	32/215	1.00 (Reference)	1.00 (Reference)	103/208	1.00 (Reference)	1.00 (Reference)
AG	165/533	1.07 (0.80-1.41)	1.06 (0.81-1.40)	76/287	1.92 (1.20-3.09)	1.70 (1.11-2.60)	89/246	0.75 (0.52-1.08)	0.78 (0.55-1.09)
GG	65/202	1.05 (0.73-1.52)	1.05 (0.74-1.50)	17/108	1.12 (0.57-2.17)	1.08 (0.63-1.86)	48/94	1.00 (0.63-1.59)	1.00 (0.66-1.52)
P_{trend}		*0.724*	*0.726*		*0.301*	*0.321*		*0.683*	*0.691*

ETS, environmental tobacco smoke; Ca, cases; Co, controls; OR, odds ratio; CI, confidence interval
[a]Adjusted for sex, age, education, income, area of residence, and exposure to ETS.
[b]Adjusted for sex, age, education, income, and area of residence.

Table 3-17. Joint associations between polymorphisms of miRNA and stem cell regulation genes and exposure to ETS on lung cancer in never smokers

	Unexposed to ETS		Exposed to ETS		Multiplicative Interaction		Additive Interaction
Gene dbSNP no.	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**ROR[a] (95% CI)**	**Bayesian Posterior ROR[a] (95% CI)**	**RERI[a] (95% CI)**
AGO2 rs4961280							
CC	1.00 (Reference)	1.00 (Reference)	1.49 (1.10-2.01)	1.45 (1.08-1.93)	0.77 (0.40-1.47)	0.81 (0.45-1.46)	-0.32 (-1.14-0.50)
CA+AA	1.15 (0.70-1.89)	1.11 (0.70-1.78)	1.31 (0.84-2.05)	1.26 (0.83-1.93)			
CTNNB1 rs2953							
TT	1.00 (Reference)	1.00 (Reference)	1.35 (0.94-1.94)	1.30 (0.93-1.83)	1.27 (0.75-2.14)	1.23 (0.75-2.01)	0.34 (-0.26-0.95)
TG+GG	0.97 (0.65-1.46)	0.93 (0.65-1.39)	1.67 (1.14-2.42)	1.60 (1.12-2.27)			
CXCL12 rs1804429							
TT	1.00 (Reference)	1.00 (Reference)	1.39 (1.05-1.84)	1.37 (1.04-1.80)	1.21 (0.52-2.78)	1.15 (0.56-2.34)	0.17 (-0.73-1.06)
TG+GG	0.82 (0.43-1.60)	0.84 (0.47-1.53)	1.38 (0.81-2.35)	1.32 (0.80-2.17)			
DDX20 rs197412							
TT	1.00 (Reference)	1.00 (Reference)	1.42 (0.96-2.10)	1.37 (0.95-1.98)	1.06 (0.63-1.80)	1.06 (0.65-1.72)	0.05 (-0.55-0.65)
TC+CC	0.93 (0.61-1.40)	0.91 (0.62-1.33)	1.40 (0.96-2.04)	1.35 (0.95-1.92)			
DICER1 rs3742330							
AA	1.00 (Reference)	1.00 (Reference)	1.69 (1.12-2.55)	1.58 (1.07-2.31)	0.76 (0.45-1.29)	0.79 (0.48-1.29)	-0.33 (-1.10-0.43)
AG+GG	1.24 (0.82-1.88)	1.17 (0.80-1.72)	1.59 (1.09-2.34)	1.50 (1.05-2.14)			
DOCK4 rs3801790							
AA	1.00 (Reference)	1.00 (Reference)	1.58 (1.03-2.43)	1.49 (1.00-2.22)	0.85 (0.50-1.46)	0.87 (0.53-1.44)	-0.21 (-0.92-0.51)
AG+GG	1.08 (0.71-1.66)	1.03 (0.70-1.53)	1.46 (0.97-2.19)	1.38 (0.95-2.01)			
E2F2 rs2075993							
GG	1.00 (Reference)	1.00 (Reference)	1.34 (0.88-2.06)	1.32 (0.88-1.96)	1.09 (0.63-1.88)	1.08 (0.65-1.79)	0.03 (-0.55-0.61)
GA+AA	0.80 (0.52-1.22)	0.80 (0.54-1.18)	1.17 (0.79-1.75)	1.15 (0.80-1.67)			
GEMIN4 rs2740348							
GG	1.00 (Reference)	1.00 (Reference)	1.46 (1.08-1.97)	1.41 (1.05-1.88)	0.76 (0.40-1.45)	0.80 (0.44-1.43)	-0.30 (-1.25-0.65)
GC+CC	1.45 (0.87-2.40)	1.36 (0.84-2.19)	1.60 (1.05-2.45)	1.51 (1.01-2.27)			

Table 3-17. Joint associations between polymorphisms of miRNA and stem cell regulation genes and exposure to ETS on lung cancer in never smokers

	Unexposed to ETS		Exposed to ETS		Multiplicative Interaction		Additive Interaction
Gene dbSNP no.	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**ROR[a] (95% CI)**	**Bayesian Posterior ROR[a] (95% CI)**	**RERI[a] (95% CI)**
GEMIN4 rs7813							
TT	1.00 (Reference)	1.00 (Reference)	2.12 (1.43-3.13)	1.91 (1.32-2.74)	0.46 (0.27-0.78)	0.50 (0.31-0.83)	-1.18 (-2.29 – -0.07)
CT+CC	2.01 (1.32-3.06)	1.81 (1.22-2.67)	1.95 (1.32-2.88)	1.76 (1.22-2.53)			
IL15 rs10519613							
CC	1.00 (Reference)	1.00 (Reference)	1.53 (0.98-2.40)	1.46 (0.96-2.20)	0.88 (0.51-1.52)	0.89 (0.54-1.49)	-0.19 (-0.89-0.50)
CA+AA	0.99 (0.64-1.51)	0.95 (0.64-1.41)	1.32 (0.89-1.98)	1.27 (0.88-1.84)			
IL6R rs4072391							
CC	1.00 (Reference)	1.00 (Reference)	1.34 (1.00-1.79)	1.33 (1.00-1.76)	1.62 (0.75-3.50)	1.44 (0.74-2.83)	0.40 (-0.32-1.12)
CT+TT	0.63 (0.33-1.19)	0.68 (0.38-1.19)	1.37 (0.87-2.16)	1.33 (0.86-2.05)			
KRAS rs9266							
CC	1.00 (Reference)	1.00 (Reference)	1.46 (1.04-2.04)	1.41 (1.03-1.94)	0.95 (0.56-1.63)	0.96 (0.58-1.58)	-0.06 (-0.71-0.59)
CT+TT	1.03 (0.68-1.56)	1.00 (0.68-1.49)	1.43 (0.97-2.09)	1.37 (0.95-1.98)			
miR-196a2 rs11614913							
TT	1.00 (Reference)	1.00 (Reference)	1.86 (1.15-3.01)	1.66 (1.07-2.56)	0.67 (0.38-1.18)	0.71 (0.42-1.20)	-0.51 (-1.44-0.42)
TC+CC	1.44 (0.92-2.27)	1.31 (0.87-1.96)	1.80 (1.17-2.77)	1.62 (1.10-2.39)			
miR-26a1 rs7372209							
CC	1.00 (Reference)	1.00 (Reference)	1.36 (0.93-1.98)	1.31 (0.92-1.87)	1.05 (0.63-1.78)	1.05 (0.64-1.71)	0.09 (-0.52-0.69)
CT+TT	1.03 (0.69-1.55)	1.00 (0.68-1.47)	1.47 (1.02-2.13)	1.42 (1.01-2.01)			
miR-27 rs895819							
TT	1.00 (Reference)	1.00 (Reference)	1.47 (1.04-2.09)	1.42 (1.02-1.97)	0.90 (0.53-1.52)	0.91 (0.56-1.49)	-0.11 (-0.77-0.56)
TC+CC	1.13 (0.75-1.70)	1.09 (0.74-1.60)	1.49 (1.03-2.17)	1.43 (1.00-2.04)			
miR-300 rs12894467							
TT	1.00 (Reference)	1.00 (Reference)	1.70 (1.20-2.42)	1.60 (1.15-2.23)	0.62 (0.36-1.06)	0.66 (0.40-1.09)	-0.62 (-1.48-0.25)
TC+CC	1.53 (1.00-2.32)	1.43 (0.96-2.12)	1.61 (1.08-2.39)	1.51 (1.04-2.19)			

Table 3-17. Joint associations between polymorphisms of miRNA and stem cell regulation genes and exposure to ETS on lung cancer in never smokers

	Unexposed to ETS		Exposed to ETS		Multiplicative Interaction		Additive Interaction
Gene dbSNP no.	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**ROR[a] (95% CI)**	**Bayesian Posterior ROR[a] (95% CI)**	**RERI[a] (95% CI)**
pre-miR-146a rs2910164							
CC	1.00 (Reference)	1.00 (Reference)	2.39 (1.49-3.83)	2.06 (1.34-3.15)	0.46 (0.26-0.81)	0.51 (0.30-0.87)	-1.20 (-2.43-0.02)
CG+GG	1.84 (1.18-2.89)	1.61 (1.07-2.41)	2.03 (1.32-3.13)	1.77 (1.20-2.61)			
RAN rs14035							
CC	1.00 (Reference)	1.00 (Reference)	1.65 (1.19-2.28)	1.61 (1.18-2.19)	0.56 (0.32-1.01)	0.61 (0.36-1.05)	-0.72 (-1.45-0.01)
CT+TT	1.04 (0.67-1.63)	1.03 (0.67-1.57)	0.97 (0.64-1.47)	0.96 (0.65-1.42)			
RBL2 rs3929							
GG	1.00 (Reference)	1.00 (Reference)	1.38 (1.01-1.89)	1.35 (1.00-1.83)	1.08 (0.61-1.91)	1.07 (0.63-1.81)	0.08 (-0.56-0.71)
GC+CC	0.93 (0.59-1.46)	0.92 (0.60-1.41)	1.39 (0.95-2.03)	1.35 (0.94-1.93)			
THBS1 rs2292305							
TT	1.00 (Reference)	1.00 (Reference)	1.19 (0.80-1.76)	1.17 (0.81-1.69)	1.36 (0.81-2.30)	1.31 (0.80-2.14)	0.32 (-0.19-0.83)
TC+CC	0.82 (0.54-1.23)	0.81 (0.56-1.19)	1.32 (0.90-1.94)	1.30 (0.90-1.86)			
TP53INP1 rs7760							
TT	1.00 (Reference)	1.00 (Reference)	1.51 (1.11-2.05)	1.48 (1.11-1.99)	0.82 (0.44-1.52)	0.84 (0.48-1.49)	-0.31 (-0.97-0.35)
TG+GG	0.87 (0.54-1.41)	0.87 (0.55-1.37)	1.07 (0.70-1.63)	1.05 (0.70-1.58)			
TP53INP1 rs896849							
TT	1.00 (Reference)	1.00 (Reference)	1.47 (1.08-2.00)	1.45 (1.08-1.95)	0.85 (0.46-1.57)	0.87 (0.50-1.53)	-0.27 (-0.90-0.35)
TC+CC	0.80 (0.50-1.29)	0.81 (0.52-1.27)	1.00 (0.65-1.53)	0.99 (0.67-1.49)			
WNT2B rs2273368							
CC	1.00 (Reference)	1.00 (Reference)	0.92 (0.57-1.47)	0.93 (0.60-1.43)	1.87 (1.07-3.28)	1.72 (1.02-2.90)	0.60 (0.17-1.02)
CT+TT	0.72 (0.46-1.11)	0.73 (0.49-1.09)	1.23 (0.81-1.86)	1.24 (0.85-1.81)			
WWOX rs12828							
GG	1.00 (Reference)	1.00 (Reference)	1.17 (0.77-1.78)	1.15 (0.78-1.70)	1.30 (0.76-2.22)	1.25 (0.76-2.07)	0.28 (-0.25-0.82)
GA+AA	0.88 (0.58-1.33)	0.87 (0.59-1.29)	1.34 (0.91-1.97)	1.31 (0.91-1.88)			

Table 3-17. Joint associations between polymorphisms of miRNA and stem cell regulation genes and exposure to ETS on lung cancer in never smokers

	Unexposed to ETS		Exposed to ETS		Multiplicative Interaction		Additive Interaction
Gene dbSNP no.	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**ROR[a] (95% CI)**	**Bayesian Posterior ROR[a] (95% CI)**	**RERI[a] (95% CI)**
XPO5 rs11077							
AA	1.00 (Reference)	1.00 (Reference)	1.53 (1.15-2.05)	1.50 (1.14-1.99)	0.49 (0.24-1.01)	0.57 (0.30-1.09)	-0.84 (-1.73-0.05)
AC+CC	1.23 (0.71-2.15)	1.19 (0.71-1.99)	0.93 (0.56-1.53)	0.92 (0.58-1.48)			
AXIN1 rs1981492							
GG	1.00 (Reference)	1.00 (Reference)	2.05 (1.38-3.04)	1.87 (1.30-2.70)	0.51 (0.30-0.87)	0.56 (0.34-0.91)	-0.97 (-1.95-0.01)
GA+AA	1.63 (1.08-2.48)	1.50 (1.02-2.21)	1.71 (1.16-2.53)	1.57 (1.09-2.26)			
AXIN2 rs2240308							
GG	1.00 (Reference)	1.00 (Reference)	1.21 (0.82-1.79)	1.18 (0.82-1.71)	1.13 (0.66-1.94)	1.11 (0.67-1.84)	0.16 (-0.43-0.74)
GA+AA	0.99 (0.65-1.51)	0.98 (0.66-1.45)	1.36 (0.93-1.98)	1.32 (0.93-1.89)			
CTBP2 rs3740535							
GG	1.00 (Reference)	1.00 (Reference)	1.46 (1.02-2.07)	1.42 (1.02-1.99)	0.95 (0.57-1.60)	0.96 (0.59-1.56)	-0.12 (-0.71-0.47)
GA+AA	0.87 (0.58-1.31)	0.86 (0.59-1.27)	1.21 (0.83-1.75)	1.18 (0.83-1.68)			
DEC1 rs2269700							
TT	1.00 (Reference)	1.00 (Reference)	1.41 (1.02-1.96)	1.37 (1.00-1.88)	0.96 (0.56-1.66)	0.97 (0.58-1.61)	-0.03 (-0.69-0.62)
TC+CC	1.05 (0.68-1.60)	1.02 (0.68-1.53)	1.43 (0.97-2.10)	1.38 (0.95-1.98)			
DLL1 rs1033583							
AA	1.00 (Reference)	1.00 (Reference)	1.45 (1.02-2.07)	1.41 (1.01-1.97)	1.02 (0.59-1.74)	1.01 (0.62-1.67)	0.00 (-0.63-0.62)
AC+CC	0.94 (0.62-1.43)	0.93 (0.62-1.37)	1.39 (0.95-2.05)	1.35 (0.93-1.94)			
DLL1 rs1421							
AA	1.00 (Reference)	1.00 (Reference)	1.53 (1.10-2.12)	1.47 (1.08-2.01)	0.80 (0.46-1.40)	0.83 (0.49-1.38)	-0.26 (-0.99-0.48)
AG+GG	1.19 (0.77-1.82)	1.14 (0.76-1.71)	1.46 (0.98-2.16)	1.39 (0.96-2.03)			
DVL2 rs222851							
AA	1.00 (Reference)	1.00 (Reference)	1.53 (1.00-2.35)	1.43 (0.96-2.13)	0.88 (0.51-1.51)	0.90 (0.54-1.48)	-0.11 (-0.83-0.61)
AG+GG	1.21 (0.79-1.84)	1.14 (0.77-1.69)	1.63 (1.09-2.44)	1.53 (1.05-2.22)			

Table 3-17. Joint associations between polymorphisms of miRNA and stem cell regulation genes and exposure to ETS on lung cancer in never smokers

	Unexposed to ETS		Exposed to ETS		Multiplicative Interaction		Additive Interaction
Gene dbSNP no.	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**ROR[a] (95% CI)**	**Bayesian Posterior ROR[a] (95% CI)**	**RERI[a] (95% CI)**
EPCAM rs1126497							
CC	1.00 (Reference)	1.00 (Reference)	1.46 (1.05-2.05)	1.40 (1.01-1.92)	0.99 (0.58-1.70)	0.99 (0.60-1.64)	0.12 (-0.65-0.88)
CT+TT	1.29 (0.84-1.97)	1.23 (0.82-1.83)	1.87 (1.28-2.73)	1.76 (1.22-2.52)			
FZD3 rs2228224							
GG	1.00 (Reference)	1.00 (Reference)	1.55 (1.08-2.22)	1.49 (1.06-2.09)	0.81 (0.48-1.37)	0.83 (0.51-1.36)	-0.27 (-0.95-0.40)
GA+AA	1.09 (0.72-1.64)	1.05 (0.72-1.55)	1.36 (0.93-1.99)	1.31 (0.91-1.88)			
FZD3 rs2241802							
GG	1.00 (Reference)	1.00 (Reference)	1.45 (0.91-2.31)	1.37 (0.89-2.09)	0.93 (0.53-1.64)	0.94 (0.56-1.59)	-0.07 (-0.76-0.62)
GA+AA	1.07 (0.69-1.67)	1.02 (0.68-1.53)	1.45 (0.95-2.21)	1.37 (0.93-2.02)			
HES2 rs11364							
GG	1.00 (Reference)	1.00 (Reference)	1.38 (0.99-1.91)	1.34 (0.98-1.84)	1.08 (0.61-1.93)	1.07 (0.63-1.82)	0.08 (-0.58-0.73)
GA+AA	0.93 (0.59-1.46)	0.92 (0.60-1.41)	1.39 (0.92-2.08)	1.34 (0.91-1.97)			
HES2 rs8708							
AA	1.00 (Reference)	1.00 (Reference)	1.55 (1.12-2.15)	1.49 (1.09-2.04)	0.84 (0.49-1.46)	0.86 (0.52-1.43)	-0.19 (-0.93-0.55)
AG+GG	1.19 (0.77-1.82)	1.14 (0.76-1.71)	1.55 (1.06-2.27)	1.48 (1.03-2.13)			
HEY1 rs1046472							
CC	1.00 (Reference)	1.00 (Reference)	1.42 (1.02-1.97)	1.40 (1.02-1.92)	1.06 (0.62-1.82)	1.05 (0.63-1.74)	-0.06 (-0.60-0.49)
CA+AA	0.72 (0.47-1.10)	0.73 (0.49-1.10)	1.08 (0.74-1.58)	1.07 (0.75-1.54)			
HEY2 rs3734637							
AA	1.00 (Reference)	1.00 (Reference)	1.49 (1.07-2.08)	1.48 (1.07-2.03)	0.91 (0.53-1.56)	0.92 (0.56-1.52)	-0.24 (-0.80-0.32)
AC+CC	0.71 (0.47-1.09)	0.73 (0.49-1.08)	0.97 (0.66-1.41)	0.97 (0.68-1.38)			
NOTCH4 rs520692							
AA	1.00 (Reference)	1.00 (Reference)	1.33 (0.98-1.82)	1.31 (0.97-1.77)	1.31 (0.72-2.37)	1.26 (0.73-2.17)	0.24 (-0.37-0.86)
AG+GG	0.78 (0.49-1.24)	0.78 (0.51-1.22)	1.35 (0.91-2.02)	1.32 (0.90-1.94)			

Table 3-17. Joint associations between polymorphisms of miRNA and stem cell regulation genes and exposure to ETS on lung cancer in never smokers

	Unexposed to ETS		Exposed to ETS		Multiplicative Interaction		Additive Interaction
Gene dbSNP no.	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**OR[a] (95% CI)**	**Bayesian Posterior OR[a] (95% CI)**	**ROR[a] (95% CI)**	**Bayesian Posterior ROR[a] (95% CI)**	**RERI[a] (95% CI)**
NOTCH4 rs915894							
CC	1.00 (Reference)	1.00 (Reference)	1.34 (0.81-2.21)	1.25 (0.79-1.96)	1.00 (0.56-1.80)	1.00 (0.58-1.72)	0.07 (-0.63-0.77)
CA+AA	1.20 (0.77-1.89)	1.13 (0.75-1.70)	1.61 (1.05-2.48)	1.51 (1.02-2.23)			
OCT4 rs13409							
CC	1.00 (Reference)	1.00 (Reference)	1.66 (1.04-2.65)	1.48 (0.97-2.26)	0.77 (0.44-1.36)	0.80 (0.48-1.35)	-0.19 (-1.06-0.68)
CT+TT	1.65 (1.05-2.58)	1.47 (0.98-2.21)	2.12 (1.37-3.27)	1.89 (1.28-2.79)			
OCT4 rs3130932							
TT	1.00 (Reference)	1.00 (Reference)	1.30 (0.89-1.91)	1.28 (0.89-1.83)	1.25 (0.74-2.11)	1.21 (0.74-1.98)	0.18 (-0.35-0.71)
TG+GG	0.78 (0.52-1.18)	0.78 (0.53-1.15)	1.26 (0.87-1.84)	1.24 (0.87-1.77)			
REX1 rs6815391							
TT	1.00 (Reference)	1.00 (Reference)	1.66 (1.08-2.54)	1.53 (1.03-2.26)	0.74 (0.43-1.27)	0.77 (0.47-1.28)	-0.33 (-1.14-0.48)
TC+CC	1.42 (0.93-2.17)	1.31 (0.89-1.95)	1.75 (1.17-2.61)	1.61 (1.11-2.34)			
WNT2 rs3729629							
GG	1.00 (Reference)	1.00 (Reference)	1.41 (0.96-2.08)	1.39 (0.97-1.99)	1.00 (0.59-1.67)	1.00 (0.61-1.62)	-0.09 (-0.66-0.48)
GC+CC	0.79 (0.53-1.19)	0.79 (0.54-1.16)	1.11 (0.76-1.63)	1.10 (0.77-1.57)			
WNT2 rs4730775							
CC	1.00 (Reference)	1.00 (Reference)	1.29 (0.91-1.83)	1.27 (0.91-1.77)	1.24 (0.73-2.10)	1.21 (0.74-1.98)	0.18 (-0.35-0.71)
CT+TT	0.78 (0.52-1.18)	0.79 (0.53-1.16)	1.25 (0.86-1.81)	1.23 (0.87-1.75)			
WNT8A rs4835761							
AA	1.00 (Reference)	1.00 (Reference)	2.25 (1.41-3.58)	1.96 (1.29-2.98)	0.51 (0.29-0.90)	0.56 (0.33-0.95)	-1.00 (-2.11-0.12)
AG+GG	1.64 (1.04-2.60)	1.45 (0.96-2.18)	1.89 (1.21-2.96)	1.66 (1.12-2.48)			

SNP, single nucleotide polymorphism; ETS, secondhand tobacco smoke; OR, odds ratio; CI, confidence interval; aROR, adjusted ratio of odds ratios; aRERI, adjusted relative excess risk due to interaction

[a]Adjusted for sex, age, education, income, and area of residence.

Table 3-18. Associations between polygenic risk score and lung cancer in never smokers by ETS exposure status

	All		Unexposed to ETS		Exposed to ETS	
Polygenic risk score	**Ca/Co**	**OR[a] (95% CI)**	**Ca/Co**	**OR[b] (95% CI)**	**Ca/Co**	**OR[b] (95% CI)**
0 (low risk)	53/269	1.00 (Reference)	17/139	1.00 (Reference)	36/130	1.00 (Reference)
1	77/281	1.57 (1.03-2.39)	31/133	2.09 (1.06-4.12)	46/148	1.34 (0.78-2.28)
2	84/242	2.12 (1.40-3.22)	29/140	1.84 (0.93-3.65)	55/102	2.40 (1.40-4.13)
3 (high risk)	117/282	2.52 (1.69-3.75)	39/151	2.38 (1.24-4.57)	78/131	2.61 (1.57-4.35)

OR, odds ratio; CI, confidence interval; ETS, environmental tobacco smoke
[a]Adjusted for sex, age, education, income, area of residence, and exposure to ETS.
[b]Adjusted for sex, age, education, income, and area of residence.

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