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Hormonal Factors in Association with Lung Cancer in Asian Women

Author
Jin, Kexin

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Hormonal Factors in Association with Lung Cancer in Asian Women

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by

Kexin Jin

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ABSTRACT OF THE DISSERTATION

Hormonal Factors in Association with Lung Cancer in Asian Women

by

Kexin Jin

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2020

Professor Zuo-Feng Zhang, Chair

Lung cancer is the most common and deadliest cancer in the world. Tobacco smoking is a leading risk factor of lung cancer. Female hormones, especially estrogen, have been suggested to be associated with the risk of lung cancer among women, compared to men, when adjusting for potential confounding factors, including smoking and environmental tobacco smoking. The effects of estrogen on lung cancer are believed to occur via estrogen receptors (ERs), which either regulate the cell proliferation or interact with lung cancer susceptibility genes. Hormonal factors (menstrual characteristics, reproductive history, and exogenous hormone use) represent the cumulative lifetime exposure to estrogen and have been studied in association with the risk of lung cancer. The current epidemiologic studies showed inconsistent results on the association between menstrual and reproductive factors and the risk of lung cancer. Population stratification, small sample size and limited power, residual confounding, and reverse causality could possibly explain the inconsistency. We conducted this study and tried to overcome the limitations of

previous studies, in order to explore potential impact of hormonal factors on the development of lung cancer.

Aim 1 of this doctoral dissertation focused on the association between menstrual/reproductive hormonal factors and the occurrence of lung cancer in the Jiangsu Four Cancers Study. We also investigated the potential gene-environment interactions between parity and genetic susceptibilities (microRNA genes, stem cell regulation genes, NF-κB pathway genes and HIF-1α pathway genes). Multivariable unconditional logistic regression models were employed in the analyses while adjusting for age, income, education, county of residence, body mass index, smoking status, pack-years of smoking, and family history of lung cancer. Among 680 female lung cancer cases and 1,808 female controls, later menopause (at >54 vs <46 years old) was associated with the development of lung cancer (semi-Bayes adjusted odds ratio, sbOR=1.61, 95% CI=1.10-2.36). More pregnancies (2 or 3 vs 0 or 1) was inversely associated with lung cancer (sbOR=0.71, 95% CI=0.53, 0.95). Ever being a smoker and having two or fewer pregnancies in one's lifetime could jointly increase the odds of lung cancer (relative excess risk due to interaction, RERI=1.71, 95% CI=0.03, 3.38). An increased number of ovulatory cycles was associated with increased probability of lung cancer (sbOR per 13 ovulatory cycles=1.02, 95% CI=1.00+, 1.04). Rs197412, a genetic variant in microRNA-related genes, showed significant different distributions between people with parity<=3 and people with parity>=4. Relative excess risk due to interaction (RERI) of rs197412 TT genotype and parity<=3 was -1.60(95% CI=-3.10, -0.10); ratio of odds ratio (ROR) was 0.34(95% CI=0.16, 0.72), indicating a sub-additive and sub-multiplicative effect modification by lower parity in the association between rs197412 (TT genotype) and the occurrence of lung cancer.

The aim 2 pooled analysis included a total of 2,456 Asian female lung cancer cases and 5,342 Asian female controls. Despite detected statistical heterogeneity, study-specific analysis showed no evident distinctions between different study designs. Therefore, a random effect of study site was integrated into the multivariable logistic regressions to allow for inter-study heterogeneities. Age, smoking status, comprehensive smoking index, and family history of lung cancer were adjusted for in the regression models. We found that late onset of menarche conferred elevated odds of lung cancer (adjusted OR= 1.16, 95% CI=1.01, 1.33 for 15-16 years old and adjusted OR=1.24, 95% CI=1.05, 1.45 for 17 years or older, compared with 14 years or younger). Late onset of menopause at 55 or older was associated with lung cancer with OR=1.24 and 95% CI=1.02, 1.51. Non-natural menopause was associated with an OR of 1.39 (95% CI=1.13, 1.71). More live births showed reversed association with lung cancer (OR of 3-4 live births=0.82, 95% CI= 0.72, 0.94, OR of 5 or more live births: 0.71 (95% CI:=0.60, 0.84), compared with 0-2 live births (P_{trend}<0.001). A later first child delivery seemed associated with an increased susceptibility: OR of 21-25 years old= 1.23 (95% CI=1.06, 1.40), OR of 26 or older=1.27 (95% CI=1.06, 1.52, P_{trend}=0.010). Oral contraceptives use appeared to be protective with an OR of 0.69 (95% CI=0.57, 0.83). Observed associations were stronger for adenocarcinoma than squamous cell carcinoma, and for published studies than unpublished ones. These relationships were not clearly modified by tobacco smoking status, probably because of lower prevalence of smoking among Asian women. This was a first and the largest pooling study of lung cancer among Asian women and the observed associations suggested potential roles of hormone-related pathways in the etiology of lung cancer.

In aim 3, in order to clarify the inconsistent results on the roles of age at menarche and age at menopause in the development of lung cancer, two-sample Mendelian randomization (MR) studies and polygenetic risk score-based analyses were carried out using published genome-wide association studies and the raw data from Female Lung Cancer Consortium in Asia. The results indicated no evident causal effect of ages at menarche (inverse-variance weighted OR per year increase=1.03, 95% CI=0.87, 1.21) and menopause (OR per year increase=1.02, 95% CI= 0.87, 1.21) on the occurrence of lung cancer, regardless of histological types. Polygenetic risk score-based analyses showed similar results.

This dissertation provided epidemiological evidence on the associations between hormonal factors and the susceptibility of lung cancer in Asian women. It confirmed the observed associations between later menarche and later menopause and increased probability of lung cancer, as well as the association between increased number of live birth and decreased probability of lung cancer, among Asian women. It also confirmed the associations between lung cancer and its susceptible genes (including microRNA genes, stem cell regulation genes, NF-κB pathway genes and HIF-1α pathway genes) in postmenopausal Asian women. In the MR analyses, ages at menarche and menopause were not showing a causal effect on lung cancer, as both ages are complicated representations of genetic and environmental factors. Parity seemed to modify the effects of lung cancer susceptible genes. These findings implied roles of hormonal factors in causal inference and risk prediction and could provide practical applications for risk population identification and personalized medicine for lung cancer.

The dissertation of Kexin Jin is approved.

Jian Yu Rao

Janet S. Sinsheimer

Alexandra M. L. Binder

Zuo-Feng Zhang, Committee Chair

University of California, Los Angeles

2020

DEDICATION

This dissertation is dedicated to my parents and grandparents.

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The aim 1 part 1 in this dissertation has been published in Translational Oncology[1]: K. Jin, M. Wu, J.Y. Zhou, J. Yang, R.Q. Han, Z.Y. Jin, A.M. Liu, X. Gu, X.F. Zhang, X.S. Wang, M. Su, X. Hu, Z. Sun, G. Li, C.H. Kim, L.N. Mu, N. He, J.K. Zhao, Z.F. Zhang, Tobacco Smoking Modifies the Association between Hormonal Factors and Lung Cancer Occurrence among Post-Menopausal Chinese Women, Translational oncology, 12 (2019) 819-827. doi: 10.1016/j.tranon.2019.03.001. Aim 1 part 2 study is in preparation for publication. The adapted contents, graphs, and tables from Aim 1 part 2 of this dissertation will be used in the manuscript for publication[2]: K. Jin, M. Wu, J.Y. Zhou, J. Yang, R.Q. Han, Z.Y. Jin, A.M. Liu, X. Gu, X.F. Zhang, X.S. Wang, M. Su, X. Hu, Z. Sun, G. Li, C.H. Kim, L.N. Mu, N. He, J.K. Zhao, Z.F. Zhang, Effect modification by parity on microRNA, cancer stem cell, NF-κB, and HIF-1α genes in association with lung cancer among post-menopausal Chinese women, (in preparation for publication), (2020). Many thanks to the Principle Investigator Dr Jin-Kou Zhao for his visionary leadership. A great amount of gratitude also goes to the collaborators (Wu, J.Y. Zhou, J. Yang, R.Q. Han, Z.Y. Jin, A.M. Liu, X. Gu, X.F. Zhang, X.S. Wang, M. Su, X. Hu, Z. Sun, G. Li, C.H. Kim, L.N. Mu, N. He, J.K.), and the Jiangsu Four Cancers Study participants, for their impactful work on rigorous study design and high-quality data collection.

The aim 2 study has been submitted and under review for publication. The adapted contents, graphs, and tables from Aim 2 of this dissertation will be used in the manuscript for publication[3]: K. Jin, R.J. Hung, S. Thomas, L. Le Marchand, K. Matsuo, A. Seow, H. Shen, J.M. Yuan, M. Wu, L. Li, J.K. Zhao, Z.F. Zhang, Hormonal factors in association with lung cancer among Asian women: a pooled analysis from the International Lung Cancer Consortium, (under review), (2020). I sincerely thank my collaborators from the International Lung Cancer Consortium. Specifically, I thank Drs Loic Le Marchand, Keitaro Matsuo, Adeline Seow, Hongbing Shen, Jian-Min Yuan, and Jin-Kou Zhao for reviewing my proposal and approving my access to data. I also thank Drs Rayjean J. Hung and Sera Thomas, who played irreplaceable roles in making this collaborative work possible and successful.

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Vita

Education

2015	Sc.M. Epidemiology, Johns Hopkins University, Baltimore, MD
2013	B.Med. Preventive Medicine, Nanjing Medical University, Nanjing (China)

Employment

2016-2019	Graduate Student Researcher, University of California, Los Angeles
2019	Teaching Associate, University of California, Los Angeles
2016-2017	Teaching Assistant, University of California, Los Angeles

Publication and conference presentations

- **Jin K**, Wu M, Zhou J, Yang J, et al. 2019. Tobacco smoking modifies the association between hormonal factors and lung cancer occurrence among post-menopausal Chinese women. *Transl Oncol*, 12(6), 819-827.
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CHAPTER 1 Background

1.1 Lung cancer

1.1.1 Lung cancer in the world and in China

Lung cancer is the most common and deadly cancer with the highest number of new cases (2,093,876) and deaths (1,761,007) according to GLOBOCAN 2018 estimation [5]. According to the CONCORD-3 study [6]and SEER project [7], the 5-year survival rate of lung cancer was 19.8% in China and 21.2% in the USA. It was also estimated that 37.0% of new lung cancer cases and 39.2% of lung cancer deaths happened in China in 2018 [8]. There were 774,323 new diagnoses of lung cancer and 690,567 deaths caused by lung cancer in 2018 in China [5] .

1.1.2 Lung cancer histology

According to the American Cancer Society[9], primary lung cancer can be divided into two categories: non-small cell lung cancer (NSCLC) and small cell lung cancer(SCLC). The frequency distribution of histologic subtypes of lung cancers is shown in Table 1-1. Adenocarcinoma may initiate in outer parts of the lung; squamous cell carcinoma (SCC) can be found in the central part of the lung, closer to the bronchus; and large cell carcinoma could start in any part of the lung. Exposure to tobacco smoking is more strongly associated with SCLC and SCC than all other lung cancer subtypes. Adenocarcinoma is the most common subtype in non-smokers and it more frequently occurs in women than in men. In terms of survival, SCLC shows the poorest survival among all other histological types.

1.1.3 Lung cancer risk factors

1.1.3.1 Age

Older age increases the risk of lung cancer. A person's cumulative exposure to carcinogens, including tobacco smoking, environmental tobacco smoke (ETS, i.e. second hand smoking), etc.), increases as he or she ages, which causes more genetic (somatic) mutations. On the other hand, the immune and DNA repair systems also slow down when a person ages. Therefore, as a person is getting older, there will be a higher probability for his tumor suppressor genes and proto-oncogenes to be mutated and thus a higher likelihood for the multistage carcinogenesis and cancer development[10].According to the American Cancer Society, about two thirds of lung cancer diagnoses occur in people older than 65 and the average age at lung cancer diagnosis is at about 70[11].

1.1.3.2 Sex

Men generally show much higher risk of lung cancer compared to women around the world. According to the GLOBOCAN 2018 estimation for lung cancer, there were 31.5 and 14.6 new male and female cases, respectively, per 100,000 people (age standardized) in the world, with male to female ratio of 2.16. In the countries with very high and high human development Index (HDI), the ASRs (age standardized rate, per 100,000 people) of incident lung cancers were 40.4 and 19.1 in men and women, respectively, with male to female ration of 2.12. In the countries with medium and low HDI, the corresponding rates were 11.8 and 4.6 with a male to female ratio of 2.57[12]. The higher risk of lung cancer in men than in women was linked to smoking habits, occupational exposures, and probably sex-related genetic susceptibilities and hormones[13-20].

1.1.3.3 Tobacco smoking

Tobacco smoking was identified as a Group 1 human carcinogen by the International Agency for Research on Cancer and was evaluated to differentially synergize with several occupational exposures (arsenic, asbestos and radon) in lung cancer carcinogenesis[21-23]. Smoking is by far the most established risk factor for lung cancer[11], with attributable risks exceeding 90% for men and close to 60% for women[24]. Compared to never-smokers, the estimated odds ratios (ORs) for lung cancer in currently smoking men and women are 23.6 (95% confidence interval, CI=20.4, 27.2) and 7.8 (95% CI=6.8, 9.0), respectively, which is reported in a large pooled analysis of 13,169 cases and 16,010 controls in 2012[25]. And an earlier large pooled analysis of 7,609 lung cancer cases and 10,431 controls showed very similar point estimates [24]. These two large-scale studies also reported consistent and much higher odds ratios of tobacco smoking (current smokers relative to non-smokers and former smokers relative to non-smokers) for SCC and SCLC than for adenocarcinoma. Taking males as an example, estimates in the 2012 pooled study were 45.7 (95% CI=29.9, 70.0), 45.6 (95% CI=34.3, 60.6), , and 10.8 (95% CI=8.7, 13.3) for male SCLC, SCC, and adenocarcinoma, respectively[25].

There were also large prospective cohort studies reporting the magnitude of risk of tobacco smoking. According to a large cohort study, the estimated hazard ratios (HR) of current cigarette smoke for men range from 20.7 (95% CI=16.3, 26.3, when the comparison is made between those who smoke 1-10 cigarettes per day and those who never smoke) to 54.9(95% CI=42.2, 71.4, when the comparison is made between those who smoke more than 40 cigarettes per day and those who never smoke). The corresponding HRs for women range from 13.4(95% CI=10.9, 16.5) to 47.3(95% CI=34.0, 65.8). .

In smokers, a higher number of pack-year [25-27] of smoking and cumulative tar exposure in tobacco products[28] shows a dose-response association with a higher risk of lung cancer. Smoking intensity (number of cigarettes per day) also increases the risk of lung cancer in this population with a dose-response trend[25].

Among never smokers, ETS is associated with increased risk of lung cancer in all histologic types (adjusted OR=1.34, 95% CI=1.24, 1.45), with the highest in small cell lung cancer (adjusted OR=1.63, 95% CI=1.31, 2.04)[27]. ETS was identified as a Group 1 human carcinogen by the International Agency for Research on Cancer in 2002.[21]

1.1.3.4 Family history of lung cancer

Familial aggregation of lung cancer might be related to two different aspects. One is the possibility of active and passive smoking exposure at home and the other is the possibility of genetic inheritance. A systematic review and meta-analysis of 28 case-controls studies and 17 cohort studies reported an estimated family history risk ratio (RR) of 1.84 (95% CI=1.64, 2.05). The increase in lung cancer risk was larger in relatives of cases diagnosed at younger ages and in those with more affected family members[29]. Genetic studies of familial aggregation, segregation, and twins have shown the inheritability of lung cancer[30]. Genetic association studies (GWAS)[31] and studies of candidate genes[32]) have provided some evidence for common risk variants of small-to-moderate effect. Linkage studies identified many rare and highly penetrant alleles. There have also been several sequencing and genomics studies providing evidence of highly penetrant germ line mutations for lung cancer[30]. Future genetic susceptibility studies of lung cancer are predicted to focus on refining the strongest risk loci in various populations, and integrating other clinical and biomarker information, in order to achieve

the aim of personalized medicine[33].

1.1.3.5 Other risk factors

Other risk factors of lung cancer include exposure to radon, asbestos, and other cancer-causing agents in the workplace, arsenic in drinking water, certain dietary supplements, radiation therapy, and air pollution.

1.2 Lung cancer in Asian women

1.2.1 Sex and racial disparity

The lung cancer incidence rate in men peaked in a number of highly developed countries around the 1980s, approximately three decades behind the peak of tobacco smoking prevalence, because lung cancer will develop and progress slowly for decades between the time of exposure to carcinogen and when cancer is detected. While lung cancer incidence rates in men have been decreasing since the 1980s, rates continued to rise among women until 2010 (Figure 1-2.)[34] and started to drop over the most recent couple of years[35].

Compared to men, women tend to have a better lung cancer survival globally. According to GLOBOCAN estimation in 2018 [5], 34.6% of new lung cancer cases and 32.7% lung cancer deaths happened in women. In women, lung cancer ranks No. 3 in incidence and No. 2 in mortality. Among never-smokers, women have increased risk of getting lung cancer but decreased probability of dying from it as compared to men[16, 19, 36, 37]. There is a higher proportion of adenocarcinoma and a lower proportion of SCC in women than in men[16]. In NSCLC patients, epidermal growth factor receptor (EGFR) mutations are more frequent in female than in male (more than 40% vs less than 15%)[38]. Among current smokers, female

patients had a 3.9-fold higher median level of CYP1A1 (*CYP1A1* gene codes Cytochrome P450, family 1, member A1 protein, a member of the cytochrome P450 enzymes) mutation compared to males[17]. After all measurable lifestyle and unchangeable factors are accounted for, the occurrences of lung cancer are still imbalanced between men and women[16, 19, 36, 37], suggesting that female sex hormones (esp. estrogen) may play possible roles in tumor initiation, promotion and progression[16, 19].

In additional to gender differences, there are also racial disparities in lung cancer. Black men are about 20% more likely to develop lung cancer (including all types) than are White men. The rate is about 10% lower in Black women than in White women[35]. Asian and Hispanic men and women showed the lowest lung cancer incidence rates, compared to Black and White populations. There's a similar pattern in the mortality rates[39]. Asian ancestry is a favorable prognostic factor for overall survival in NSCLC, independent of smoking status[40]. Compared with Caucasian patients with NSCLC, East Asian patients show a much higher prevalence of epidermal growth factor receptor (EGFR) mutation (approximately 30% vs. 7%, predominantly among patients with adenocarcinoma and never-smokers), a lower prevalence of K-Ras mutation (less than 10% vs. 18%, predominantly among smokers and patients with adenocarcinoma and smokers), and a higher proportion of patients who are responsive to EGFR tyrosine kinase inhibitors (EGFR-TKIs) [40].

EGFR-TKIs (gefitinib, erlotinib, and afatinib) have shown high progression-free survival benefit with a negligible toxicity compared to cytotoxic chemotherapy. Lung adenocarcinoma patients with genetic mutations in EGFR exons 19 and 21 have been observed highly responsive to EGFR-TKIs. Therefore, these EGFR-TKIs have been used as first-line treatment for lung

adenocarcinoma patients with corresponding EGFR mutations[41, 42]. It is important to learn the EGFR mutations among non-smoking Asian women with adenocarcinoma and EGFR mutations since EGFR mutation rates in lung cancer are generally higher in Asian compared with Western populations, non-smokers compared with smokers, women compared with men, and adenocarcinoma compare with other histological subtypes[43, 44].

1.2.2 Biological mechanism of estrogen effects on lung cancer

Hormonal factors, especially estrogen, have been suggested to explain the gender gap in the risk of lung cancer, that remains after adjusting for lifestyle factors, including smoking and environmental tobacco smoking [37]. The effects of estrogen on lung cancer are believed determined by estrogen receptors (ERs). Estrogen receptor α and β (ERα and ERβ), the two major types of ERs, are found in bronchial and alveolar epithelia and airway smooth muscle[16]. There are two estrogen receptor related signaling pathways that could explain the effect of estrogen on lung cancer.

1.2.2.1 Estrogen receptors as transcription factors

One of the signaling pathways starts with the binding of 17-β estradiol (E2, the activation form of estrogen in humans) to ERs, which leads to dimerization and nuclear translocation of theses ERs. Both ERα and ERβ are ligand-activating transcription factors that are activated by E2. In the nucleus, ligand-bound ERα/ERβ dimers bind to the estrogen response elements (ERE) in the promoters of target genes to control cell proliferation, differentiation and apoptosis. ERs can also interact with other transcription factor complexes and thus indirectly influence gene transcription[15, 45].

1.2.2.2 EGFR pathway

Besides this classical estrogen signaling pathway mentioned above, there is an alternative carcinogenic pathway involving epidermal growth factor receptor (EGFR). In this pathway, the ligand-bound ERs are believed to translocate from the cytoplasm to the cell membrane where they associate with and activates EGFR, the receptor tyrosine kinase. Activation of EGFR triggers the MAPK/ERK (mitogen-activated protein kinases/extracellular signal-regulated kinases) pathway, which results in ERK migrating to the nucleus and up/down regulating the transcription of genes that promote proliferation and invasion of lung cancer cells[15, 46, 47].

1.2.3 Epidemiologic evidence of hormonal effect on lung cancer

The circulating estrogen and exogenous estrogen are the main sources of ER ligands, and their level determines the strength of the effect of ERs on cell proliferation and carcinogenesis. However, the level of circulating and exogenous estrogens varies by day in the menstrual cycle and the time of a day. Menstrual and reproductive factors are regarded as proxies for life-long endogenous estrogen exposure in women, while oral contraceptive use (OC) and hormone replacement therapy (HRT) represent exogenous sources of estrogen. Menstrual factors include age at menarche and menopause, length of menstrual cycle, menstrual cycle regularity and reproductive window. Reproductive factors include parity and gravidity, ages and outcomes of births, and breastfeeding.

Between 1988 and 2020, there have been more than 20 observational epidemiologic studies (case-control studies and cohort studies) on a variety of menstrual, reproductive, and hormonal factors and the risk of lung cancer. These studies (not including the ones in this dissertation) were published in two ILCCO (International Lung Cancer Consortium) pooled analysis in 2017

and 2013[48, 49], three meta-analysis in 2019 and 2012[50-52], six individual studies[53-58] after 2012, and several others before 2012[59-65]. The estimated association between endogenous and exogenous estrogen exposure and lung cancer has been inconsistent. A cumulative lifetime exposure to endogenous estrogen could possibly explain many results from these studies. However, the effect of exogenous hormone is inconsistent across studies due to racial heterogeneity and other unknown reasons. Except length of menstrual cycle, there was barely consistent association found between other hormonal factors and lung cancer risk in the published studies. A summary of the findings is shown in Table 1-2. Except the meta-analyses, all other publications provided risk estimates adjusted for confounding variables.

1.2.3.1 Menstrual characteristics and lung cancer

1.2.3.1.1 Age at menarche

Older menarcheal age has been hypothesized to be protective against lung cancer occurrence because older menarcheal age may be related to a lower lifetime exposure to endogenous estrogen. Several studies looked at the association between age at menarche and lung cancer incidence; however, only the 2012 meta-analysis showed statistically significant results. In this meta-analysis of 16 case-control and 8 cohort studies (or nested case-control studies), a decreased risk of lung cancer in women with older age at menarche was found among populations of European descendants. This study also showed that later age at menarche was associated with a 17% decreased risk of lung cancer (highest vs youngest age group for menarche, RR=0.83, 95% CI=0.73, 0.94).

1.2.3.1.2 Age at menopause and reproductive window

The relationship between menopausal age and risk of lung cancer has also been inconsistent. The 2015 Women's Health Initiative (WHI) study observed a protective effect of later age at

menopause (OR for 50+ vs <40 years old =0.73, 95% CI=0.62, 0.85)[53]. However, a cohort study[55] and two case-control studies[54, 58] in Asia reported significantly increased hazard or odds among people with a later menopause. Two cohort studies in Asia (Singapore and Korea)[56, 57], a meta-analysis[50], and two pooled analyses[48, 49] did not find a clear association between age at menopause and lung cancer. A tabular summary of these findings were presented in Table 1-2. .

There were three studies conducted in Asia on reproductive window, the number of years between menarche and menopause. None of them showed any meaningful association[54-56].

1.2.3.1.3 Menstrual cycle length

A longer menstrual cycle length has been hypothesized to be associated with reduced risk of lung cancer. A longer menstrual cycle results in fewer menstrual cycles in one's life, leading to reduced exposure to the estrogen surge at ovulation. Two studies reported a decreased risk among people with a longer length of menstrual cycle[50, 54]. Menstrual cycle length was the first menstrual/reproductive factor that has been found being associated with the risk of lung cancer(adenocarcinoma)[65] and since then (1987), more and more studies were conducted addressing menstrual/reproductive factors.

1.2.3.2 Reproductive history and lung cancer

1.2.3.2.1 Parity/gravidity and number of birth

Gravidity and parity are the numbers of times a female is or has been pregnant and carried the pregnancies to a viable gestational age, respectively. Only times of pregnancies are counted and twin pregnancy is counted as one[66]. Gravidity and parity represent estrogen surge in a period of time. They also represent a reduced ovulation and a decrease in number of natural cycle of

estrogen change. In epidemiology, parity usually includes live births and stillbirths, and gravidity includes all live births, stillbirths, induced abortions and miscarriages.

Parity/gravidity/number of children have been positively associated with the risk of lung cancer among populations of European descendants(Table 1-2)[48, 49, 53] In Asian women, these factors were either inversely associated with or not found associated with the risk of lung cancer[54-58]. In mixed populations, results were null or borderline significant[50, 52].

1.2.3.2.2 Types of contraception

Different types of contraception have shown varied effects on lung cancer. Oral contraceptive use (OC), intrauterine device (IUD), ligation and condoms are the major method of birth control. The 2017 ILCCO pooled analysis observed a protective effect of OC use on the development of lung cancer (OR=0.81, 95% CI: 0.68-0.97)[48]. The 2013 Shanghai study of textile workers found that tubal ligation was associated with a 17% (HR=0.83, 95%CI= 0.72, 0.97) decreased hazard of lung cancer [55]. The effect of ligation could be explained by the decrease of estrogen by blockage of fallopian tube[67]. IUD is the most effective long-acting reversible contraception and is proved to reduce the risk of endometrial and cervix diseases, including cancers. [68, 69]. IUD was not found to be associated with risk of lung cancer in the 2013 Shanghai study[55].

1.2.3.2.3 Number of ovulatory cycles

The association between ovulatory/menstrual cycles and the risk of lung cancer was firstly looked at in postmenopausal breast cancer[70]. To estimate lifetime number of ovulatory cycles, people subtracted the duration of oral contraceptive use, 36 weeks for each live birth, 28 weeks for each stillbirth pregnancy, and 12 weeks for each miscarriage/abortion from the number of

reproductive years[70, 71]. There has been no epidemiologic study looking at number of ovulatory/menstrual cycles and lung cancer yet.

1.2.3.3 Exogenous hormone and risk of lung cancer: OC and HRT

OC seems to exert different influences in populations of European and Asian descendants. In ILCCO pooled analysis, OR of OC was 0.81, with a 95% CI of 0.68-0.97; [49]. On the contrary, in a case-control study in China, OC use was found to be associated with increased probability of lung cancer occurrence (OR=1.84, 95% CI=1.11, 3.06)[58]. Different from OC use, HRT showed associations with lung cancer in various types of epidemiologic studies. A meta-analysis of 13 cohort studies resulted in a reverse association between HRT and the risk of lung cancer (RR= 0.95, 95% CI=0.91, 0.99)[51]. The ILCCO pooled analysis of 6 case-control studies reported the summary OR of 0.77(95% CI=0.61, 0.94) for HRT[49]. The combined analysis of clinical trials and observational studies in WHI showed that the HR of more than 5 years previous estrogen plus progestin use, comparing with nonuser, was 0.84 (95% CI=0.72, 0.98)[53]. In four studies of Asian population and the meta-analysis of a mixed population, no clear association was observed due to small numbers of women with the use of OC or HRT[54-57].

1.3 Genetic susceptibility and gene-environment interactions with menstrual/reproductive factors on lung cancer in Asian women

As discussed in **1.2.1 Sex and racial disparity**, genetic susceptibility might differ by sex and race.

1.3.1 microRNA

MicroRNAs (miRNAs) are single-stranded, non-coding RNAs composed of about 22 nucleotides. More than 50% of human genes are possible targets of microRNA regulation[72-

75]. Many enzymes and proteins are involved in microRNA processing. Drosha (a Class 2 ribonuclease III enzyme, encoded by the *DROSHA* gene) processes the RNA precursors into pre-microRNAs in the nucleus[76-78]. The pre-microRNAs are then transported to the cytoplasm via XPO5 (exportin 5, encoded by the *XPO5* gene) with the energy provided by RAN (RAs-related Nuclear protein, encoded by the *RAN* gene) GTPase[79]. In the cytoplasm, pre-microRNAs are further transformed into the mature microRNA, which are double-strand microRNAs, by Dicer (endoribonuclease Dicer or helicase with RNase motif, encoded by the *DICER1* gene). One of the microRNA double strands is then integrated into the RISC (RNA induced silencing complex, which is composed of the Argonaute proteins, Gemin3 and Genmin4, and so on) and base-pairs imperfectly with its target mRNA [80]. Therefore, RISC degrades or represses the translation of its target mRNAs, which is the mechanism of microRNAs regulated gene expression[81, 82]. There are two types of microRNAs. Oncomirs inhibit the expression of tumor suppressor genes, whereas tumor-suppressing microRNAs enhance the expression of oncogenes[83].

1.3.2 Stem cell regulation

Cancer stem cells (CSCs) are regarded as a distinct population in cancer cells which renew themselves and persist. They are believed to be responsible for cancer metastasis and relapse. Signaling pathways of Wingless-type protein (Wnt), Hedgehog, and Notch have been identified as key regulators of stem cells[84]. Polymorphisms of genes involved in these pathways play roles in carcinogenesis. *EPCAM* rs1126497, *HEY1* rs1046472, *HEY2* rs3734637, *OCT4* rs13409, and *WNT2* rs3729629 have been associated with the risk of lung cancer among never smokers in a Chinese population[72]. The same study also detected statistical interaction of *GEMIN4* rs7813 (multiplicative and additive), *WNT2B* rs2273368 (multiplicative and additive), *pre-miR-a46*

rs2910164 (multiplicative), *AXIN* rs1981492 (multiplicative), and *WNT8A* rs4835761 (multiplicative) by ETS on the risk of lung cancer. The biological explanation of AXIN (axis inhibition protein) could be a deregulation of Wnt signaling pathway, the most important pathway in stem cell regulation[72, 85]. The Wnt glycoprotein binds to Frizzled (Fz) receptors, stabilizing and locating β-catenin into the nucleus. β-catenin binds to transcription factors and regulates the expression of target genes[86-90]. The interaction between sex hormones and wnt/β-catenin signaling pathway has been suggested in cancer development; it has only been studied in endometrial diseases and has not been studied in lung cancer[91].

1.3.3 NF-κB pathway

NF-κB (nuclear factor κ-light-chain-enhancer of activated B cells, encoded by the *NFKB1* and *NFKB2* genes) is a protein complex and a transcription factor involved in the regulation of genes controlling cell proliferation and survival. Deregulation of NF-κB has been linked to cancer and many other diseases. While in an inactivated state, NF-κBs are inhibited and localized by the inhibitory protein IκBα (NF-κB inhibitor α, or nuclear factor of κ light polypeptide gene enhancer in B-cells inhibitor, α; encoded by the *NFKBIA* gene) in the cytoplasm. If activated, the trans membrane signals activate the enzyme IκB kinase (IKK) to phosphorylate IκBα, letting it be degraded by proteasomes. The activated NF-κB heterodimer will then be imported into the nucleus and bind to the response elements in the promoter regions of target genes, thus up- or down-regulating the transcription of target genes. The *IKBKAP* gene is very important in providing guidance in the formation of the IKAP protein complex of NF-κB heterodimer, IKK and IκBα[92-97].

Estrogen and related metabolites have been suggested to interact via the NF-κB Pathway to increase cyclooxygenase 2 (COX-2) expression and prostaglandin E2 (PGE2) secretion in cultured human bronchial epithelial cells. Increased COX-2 and PGE2 secretion has been shown to increase the risk of cancer occurrence[98].

1.3.4 HIF-1α pathway

HIF-1α (Hypoxia-inducible factor 1- α, encoded by the *HIF1A* gene) is a subunit of HIF-1, a transcription factor. Dysregulation of the *HIF1A* gene has been related to increased overall cancer risk in epidemiologic studies[99, 100]. There have been a few studies on the *HIFA* gene polymorphisms and risk/survival of lung cancer as well as gene-environment interaction (G by E) by cigarette smoking[73, 101]. However, there was no G by E study of the *HIFA* gene and reproductive factors on the risk of lung cancer.

1.4. Causal inference and Mendelian randomization

There are two categories of traditional epidemiologic studies: observational studies and randomized controlled trials (RCT)[102]. Because HRT used in randomized intervention trials only represents exogenous exposure to estrogen and cannot represent endogenous hormonal effect, observation studies such as case-control and cohort studies are most commonly used study design on the relationship between steroid hormone levels and lung cancer risk. However, confounding, bias and temporality are the most important issues of validity in observational studies.

1.4.1 Temporality and reverse causality

In case-control studies of female hormonal factors and the risk of lung cancer, when the self-reported information on menstrual and reproductive history, and exogenous hormone use is collected, the person could already been diagnosed with lung cancer and could have undergone

chemotherapy. Because of the menopause resulted from chemotherapy, the parity could be fewer than that of people without a lung cancer diagnosis. Therefore, it cannot be verified if reduced parity is due to lung cancer or if it is due to chemotherapy after lung cancer diagnosis. Different types of causal inference tools could improve the temporality and reverse causality in observational studies[103-106].

1.4.2 Residual confounding

Confounding is a major concern in epidemiology. There are multiple ways to control for confounding in traditional epidemiologic studies. Randomization, restriction, and matching are the three ways to control for confounding variables at the stage of study design. In traditional epidemiologic studies, stratifying and multivariable models are used during the analysis stage[107]. In the Aim 1 of this dissertation, stratification by smoking status and multivariable logistic regressions were applied in order to control for smoking and other known risk factors of lung cancer. Exposure scoring (i.e., propensity scoring), outcome scoring (i.e., prognostic scoring or disease risk scoring) [108, 109], inverse probability weighting, and g-computation could also handle the confounding issues. All of these methods require accurate measurements of the potential confounding factors (Z in Figure 1-3) in order to obtain valid effect estimates of the exposures of interest[103-105].

There have been several cohort studies on the association between reproductive factors and the risk of lung cancer. Many of them found associations between age at menopause[53, 63, 110-112] and the risk of lung cancer. Some others found associations between parity and lung cancer[53, 55, 56, 59, 62, 110, 113]. There is generally less concern about temporality in prospective cohort studies; however, residual confounding of smoking cannot be ruled out and

could potentially distort the true association. In some studies, there was no data on ETS[53, 55, 56, 59, 62, 110, 111], which is a strong risk factor of lung cancer and might affect menstrual cycles[27, 114]. ETS is also much more prevalent in female non-smokers than in males or smokers. The cumulative effect of smoking was analyzed in these studies either using pack-year of smoking[53, 62, 112], duration of smoking[54], or intensity (cigarettes per day)[56, 59]. The 2017 ILCCO pooled study applied the Comprehensive Smoking Index (CSI), which incorporated measures of smoking duration, time since cessation, and smoking intensity into one aggregate measure[48]. Other studies did not account for the duration or intensity of exposure to smoking, giving rise to potential residual confounding[115, 116]. Despite all these measures of smoking, residual confounding of tobacco smoking could still exist considerably and might obfuscate the observed association given the strong impact of smoking on lung cancer. Most of the studies did not have measures on cooking fumes or indoor air pollution, which could also be very important for studies of lung cancer among women.

Body mass index (BMI) is another factor in the causal pathway between hormonal factors and lung cancer. It could be regarded as a mediator since hormonal factors are associated with BMI and BMI is associated with the risk of lung cancer. However, in the directed acyclic graph (DAG), the direction of the arrow between BMI and lung cancer could be directional. Epidemiologic evidence has shown the association between BMI and lung cancer. It has been hypothesized that excess body weight and obesity are protective factors against lung cancer in current and former smokers (No association was found between BMI and lung cancer risk among non-smokers.)[117]. On the other hand, the development of lung cancer could cause a decrease in BMI[106]. Therefore, BMI could either be a mediator or a collider in the DAG.

1.4.3 Causal inference tools addressing temporality and residual confounding

In order to overcome residual confounding and reverse causation, instrumental variable (IV) analysis was adopted by epidemiologists from econometric research in the1990s[118]. All methods for confounding control mentioned in **1.4.1 Temporality** or **1.4.2 Residual confounding** require the information of the potential confounders be collected; however, in real situations, potential confounders are either unknown or are difficult to be measured accurately. IV analysis has been used to remove all measured and unmeasured confounding factors[118]. Mendelian randomization (MR) is a type of IV analysis that takes advantage of the fact that homologous chromosomes are randomly separated into two daughter cells during meiosis according to Mendel's Second Genetic Law. MR is therefore regarded as a 'natural' experiment and can solve the problem of residual confounding and reverse causation[119-123]. As shown in the DAG in Figure 3, the genetic variant G is a valid instrument if:

1) G, the genetic variant and the IV, is associated with E, the exposure;

2) Except population stratification, there is no measured/unmeasured/known/unknown variable that confounds the association between G and D, the disease outcome (this assumption is always true since genetic variants happen prior to all other variables. Therefore, Z could not affect G because G always precedes Z);

3) G is associated with D only through E (i.e., there are no other open pathways from G to D than G→E→D in the DAG)

Given these conditions are met, ratio of the coefficient of E(D|G) and the coefficient of E(E|G) is a consistent estimator of the causal effect of E(D|E)[123].

There are several limitations of Mendelian randomization, which were revisited in Chapter 4 Discussion[123, 124]:

1) Lack of suitable polymorphisms for studying modifiable exposures of interest;
2) Failure to establish reliable genotype—intermediate phenotype or genotype—disease associations
3) Confounding of genotype—intermediate phenotype—disease associations, esp. population stratification and other genes in linkage disequilibrium
4) Pleiotropy: one gene could have multiple functions thus influence the risk of outcome through pathways other than the one involving the exposure of interest
5) Canalization (developmental compensation): the buffering of the effects of genetic variation during development

CHAPTER 2 Objectives and Methods

2.1 Objectives

The overall objective of this dissertation was to explore the role of hormonal factors in the development of lung cancer among Asian women. We focused on three categories of exposures: menstrual characteristics, childbearing history, and exogenous hormone use. We evaluated the association between these factors and lung cancer in a Chinese post-menopausal population, a pooled Asian population, and a Mendelian randomization study. We explored potential effect measure modifications of active tobacco smoking. We also investigated microRNA regulation, stem cell regulation, NFκB, and HIF-1α related genetic susceptibility, and their joint effect with parity in our population.

2.2 Aims and hypotheses

2.2.1 Aim 1 Association of menstrual/reproductive factors and candidate genes with risk of lung cancer and potential gene-environmental interactions among Chinese women

The hypotheses of this study are:

1) More menstrual cycles and a fewer number of pregnancies are associated with increased susceptibility of lung cancer among postmenopausal Chinese women
2) The association between exposure to menstrual cycles/number of pregnancies and lung cancer among postmenopausal Chinese women is modified by smoking status
3) Genetic polymorphisms in microRNA regulation, stem cell regulation, NFκB, and HIF1- α pathways are associated with lung cancer among postmenopausal Chinese women

4) There are potential gene-environmental interactions or joint effects between menstrual/reproductive factors (e.g., parity as a binary variable) and candidate SNPs in the development of lung cancer

2.2.2 Aim 2 Association between hormonal factors and lung cancer in Asian women: a pooled analysis from the International Lung Cancer Consortium

The hypotheses of this study are:

1) Age at menarche and age at menopause are associated with lung cancer in Asian populations
2) Number of childbirths and age at first birth are associated with lung cancer in Asian descendants
3) Use of oral contraceptives and hormone replacement therapy are associated with lung cancer in Asian women
4) The direction and magnitude of the associations are heterogeneous between adenocarcinoma and squamous cell carcinoma
5) The direction and magnitude of the associations are heterogeneous between smokers and non-smokers
6) The direction and magnitude of the associations are heterogeneous between published studies and unpublished studies

2.2.3 Aim 3 Mendelian randomization study of age at menarche and age at menopause and the risk of lung cancer

The hypotheses of this study are:

1) Older ages at menarche increases the susceptibility of lung cancer in Asian descendants
2) Older ages at menopause increases the susceptibility of lung cancer in Asian descendants

2.3 Study population and Design

2.3.1 Aim 1

The Jiangsu Four Cancers (JFC) study is a large-scale, community-based case-control study of cancers of the lung, liver, stomach, and esophagus in a Chinese population. It was carried out in an effort to obtain consistent and high-quality data to investigate the lifestyle, behavioral, environmental, and genetic factors associated with the four major cancers in China[125].

Between 1 January 2003 and 31 December 2010, incident female primary lung cancer cases were reported in the CDC-managed cancer registries of four counties in Jiangsu Province in China. The four counties were Chuzhou, Dafeng, Ganyu, and Tongshan. Diagnoses were either pathologically or clinically confirmed within one year of interview. Cases were required to be at least 18 years old, residents of the respective county for at least 5 years, and in a stable medical condition as determined by their physicians. The participation rate was 43% among lung cancer cases in the JFC study[125]. Premenopausal cases were excluded in data analyses. There was a total of 680 cases eligible for this study of menstrual and reproductive factors in association with lung cancer.

Controls of the JFC study were females randomly selected from the same village or resident block as the cases. The JFC study individually matched controls to cases by age (+/- 5 years). The participation rate was 87% among the controls in the JFC study[125]. In the current analysis, all postmenopausal female controls of 4 cancer sites were combined in order to increase power. Premenopausal controls were excluded during data analyses. A total of 1,808 controls were

eligible for the analysis. The JFC study had IRB (institutional review board) approval and informed consent from all participants collected before study enrollment.

2.3.2 Aim 2

This analysis included six studies with Asian women within ILCCO (http://ilcco.iarc.fr/index.php), which was established in 2004 with the aim of sharing comparable data from ongoing case-control or cohort studies on lung cancer [126]. The criteria for inclusion in this pooled analysis were: 1) either case-control or nested case-control designs with clinically or pathologically confirmed lung cancer cases; 2) written agreement to contribute data on individual subject level; 3) female subjects whose origins are Asia; 4) availability of information on hormonal factors (menstrual characteristics, childbearing history, and exogenous hormone use) and covariates (age, smoking history, and family history of lung cancer in first-degree relatives) collected for individual subjects; and 5) at least 100 eligible lung cancer cases in the study. Four case-control studies were included such as Genes and Environment in Lung Cancer I (GEL1) [127], Aichi Study[128], Nanjing Lung Cancer Study (NJLCS) [129], and Jiangsu Four Cancers Study (JFC) [130]. The controls were sampled from general population in JFC and NJLCS, while Aichi and GEL1 were hospital-based. All four case-control studies frequency-matched controls to cases on age. In addition, GEL1 matched on hospital and period of hospital visit, and NJLCS and JFC both matched on residence. Two cohort studies included, Singapore Chinese Health Study (SCHS) [131] and Multiethnic Cohort Study (MEC, Japanese American women only) [132], were analyzed as nested case-control studies. In these two studies, incidence density sampling method (case to control ratio=1:2) was applied, in order to obtain more accurate odds ratio estimates for lung cancer. Age was used as the time scale for these two studies. When a lung cancer case was diagnosed, two participants from the same cohort were

randomly selected as controls for the lung cancer case, if those two subjects were lung cancer-free at the age when the case was diagnosed. Because MEC and SCHS did not require participants to be cancer-free at study entry, to ensure cases were event-free at entry, and to reduce potential misclassification bias, a case was included only if her follow-up time (person-year) in this pooled study is as least 2 person-years. In order to keep similar average follow-up time for cases and controls, a control was also only included if she has at least 2 person-years of follow-up in this study. (A case was excluded in this pooled study if the age difference between her study entry and her lung cancer diagnosis was less than 2 years. Similarly, a potential control was removed from the risk set if the difference between her age at study entry and her age at matching (i.e. the age at which the corresponding subject case was diagnosed with lung cancer) was less than 2 years.) Studies included in this analyses were all approved by their institutional review board and informed consents were collected from human participants. De-identified epidemiological data had been cleaned, harmonized, and pooled at individual level at ILCCO data repository and University of California, Los Angeles. The Institutional Review Board Exemption was obtained (IRB#19-001513) at University of California, Los Angeles.

2.3.3 Aim 3

Two-sample summary-data MRs and polygenetic risk score (PRS)-based analysis were conducted. SNPs identified from published primary GWA studies[133-147] were used as genetic IVs for both Step 1 and Step 2 in the two-sample MRs and PRS-based analysis. The raw data for Female Lung Cancer Consortium in Asia (FLCCA) [148] from Genotypes and Phenotypes (dbGaP), were used in the Step 2 in the two-sample MRs.

The genetic data derived from the FLCCA [148], a GWA study composed of 4,922 never-smoking female lung cancer cases and 3,959 controls. All participants were drawn from 14 studies from Mainland China, South Korea, Japan, Singapore, Taiwan and Hong Kong. All cases were histologically confirmed. The genotyping data of this GWA is available on the National Institute of Health (NIH) database dbGaP (study accession: phs000716.v1.p1). Phenotype data included in this database were age categories, case/control status, and histological types of cases. Information on the traits of interest in this study (age at menarche and age at menopause) was not collected in this GWA.

2.4 Epidemiologic data collection

2.4.1 Aim 1

A standardized epidemiological questionnaire including demographic characteristics, social economic status and menstrual/reproductive history, and other risk or protective factors was employed to collect data for both cases and controls by face-to-face interview. The interviewers were trained and the questionnaire was field tested in a previous study[149]. Five percent of the face-to-face interviews were conducted twice to verify the quality of the data. The questionnaire data collected from the first interview was reviewed by a research staff member at the county level and then by an epidemiologist at the provincial CDC. Data was doubly entered into an epidemiology database designed using EpiData (Odense, Denmark) at each county CDC and then the data was cleaned and managed at Jiangsu Provincial CDC[92]. For this dissertation project, we used variables such as age, smoking, ETS, family history of lung cancer, and menstrual/reproductive factors. In this dissertation project, a variable was coded as missing if the participant had inconsistent answers by cross-checking related questions or repeated questions

for the variable.

Exposures of interest included age at menarche, age at first birth, parity, gravidity, breastfeeding, oral contraceptive use, measures of birth control, outcome of first pregnancy, miscarriage, induced abortion, stillbirth, and live birth. Reproductive window and number of ovulatory cycles were estimated accordingly. The outliers (impossible and inconsistent information) of ages at menarche, menopause, and first birth, as well as contradictory answers in reference to current age, were treated as missing data. The normalized distributions of those menstrual and reproductive ages were adapted from large observational studies conducted in China among women with similar years of births in the JFC study[150, 151]. Reproductive window was calculated as the difference between age at menopause and menarche. Gravidity and parity are the numbers of times a female has been pregnant and carried the pregnancies to a viable gestational age, respectively. Gravidity was calculated as the sum of numbers of miscarriages, abortions, live births, stillbirths, and all other outcomes of pregnancy. Parity was calculated as the sum of live births, and stillbirths[66]. Missing data in number of live births, miscarriages, induced abortions and stillbirths were imputed with the median in the control group. The number of ovulatory cycles was calculated[70, 71] based on the reproductive window, subtracted by the length of no ovulation due to OC use, live births, stillbirths, miscarriages, induced abortions, and breast feeding. It was calculated assuming 36, 28, 12, and 12 weeks of no ovulatory cycles by virtue of a live birth, a stillbirth, a miscarriage, and an induced abortion, respectively. It was also assumed that there was no ovulation during oral contraceptive use (OC). If the participant's answer to the breastfeeding question was 'breast feeding only', 'no breast feeding', or 'mixed feeding', the length of time without ovulatory cycles after delivery was assumed to be 24, six,

and nine months, respectively. 28 days was applied as the average length of an ovulatory cycle and 52.178 weeks in a year was assumed.

Covariates included age at interview, body mass index (BMI, categorization for Chinese), binary smoking status, binary ETS status, pack-years of smoking, family history of lung cancer (binary), income (categorical), education (categorical), and county. Age of the participants were self-reported and checked with the interviewer. If the participant only remembered the lunar month of birth, the following solar month was used as the proxy. There were no missing data for year of birth. In cases of missing month or date of birth, the median values (July and 15th) were used as the estimations. BMI cut points were chosen for underweight (<18.5), overweight (>=18.5 and <24), and obesity (>=28) according to the standards for Chinese populations[152]. Ever-smoking was defined as having smoked more than 100 cigarettes in one's lifetime. Exposure to ETS included passive smoking at home and at work. ETS at home was defined as having been exposed to smoking from family members for no less than one to two days/week for at least one year. ETS at work was defined as having been exposed to ETS in working environment for more than 15 min/day, no less than 1-2 day/week, and no less than one year. Missing values for pack-years (missing rate=12.6%) of smoking were imputed with the county, sex, and age specific median value of the controls. Family history of lung cancer was defined as lung cancer diagnosis in any family members including parents, grandparents, siblings, children, spouses, and parents' siblings. Incomes were defined as the per-capita annual income of the household including wages, bonuses, and allowances on an average over the most recent decade.

2.4.2 Aim 2

All cases had confirmed diagnoses of primary lung cancer either pathologically or clinically. The histological classification in this study was based on the International Classification of Diseases for Oncology (ICD-O) version 2 and the International Classification of Diseases (ICD), Ninth or Tenth Edition. Individual study subjects were interviewed using separate structured questionnaires at each study site. Hormonal factors information collected includes age at menarche, menopausal status, reason and age at menopause, number of childbirths, age and outcome at first childbirth, use of oral contraceptives (OC) and use of hormonal replacement therapy (HRT). Menopause due to oophorectomy (removal of both ovaries), hysterectomy, radiation, or chemotherapy was classified as non-natural menopause. Reproductive window was defined as the length of duration (years) between age at menarche and age at menopause. HRT included use of either estrogen- or progestin-containing therapies. An individual study was eligible for the pooled analysis on an exposure variable if this variable was collected for at least 70% in that population in order to ensure relatively low overall missing data in the pooled analysis. Age was defined as age at diagnosis for a lung cancer case and that at interview for a control in the four case-control studies. In the two nested case-control studies, age was defined as the age at matching (i.e. the age at which the subject case was diagnosed with lung cancer) for both cases and controls. Never smokers were defined as those who smoked less than 365 cigarettes in their lifetime in GEL1 study, as self-reported never smoked in Aichi study, as those who smoked less than 20 packs of cigarettes in their lifetime in MEC, and as those who smoked less than 100 cigarettes in their lifetime in other studies. Former smokers were defined as those who had stopped smoking for at least 2 years prior to the recruitment. To address the cumulative

effect of lifetime tobacco smoking, the comprehensive smoking index (CSI) [153] was calculated. CSI is a comprehensive measure that takes into account the smoking intensity (number of cigarettes per day), duration of smoking (years), and time since smoking cessation (years). If one assumes that a subject has started smoking 'tss' (time since starting) years ago and stopped smoking 'tsc' (time since cessation) years ago (tss>tsc), with a constant intensity (number of cigarettes smoked per day), then the total impact of smoking exposure can be quantified as:

$$\int_{tsc}^{tss} a \cdot 0.5^{\frac{t}{\tau}}\, dt = a \cdot \tau \cdot (\ln 2)^{-1} \cdot (0.5^{\frac{tsc}{\tau}} - 0.5^{\frac{tss}{\tau}})$$

Omitting constants that do not depend on tsc, the individual level of smoking exposure, and multiplying by the constant intensity (int), yields CSI

$$= \left(1 - 0.5^{\frac{dur^*}{\tau}}\right)\left(0.5^{\frac{tsc^*}{\tau}}\right) \ln\,(int + 1)$$

τ is the half-life of smoking impact. AIC (Akaike information criterion) has been used to evaluate the goodness of fit of the model. Covariates to be adjusted for in the regression models were measured in all the six individual studies. All data were crosschecked for inconsistency. Inadmissible values and outliers were set as missing after confirmation with the original individual principle investigators and/or data coordinators for all studies.

2.5 Genetic data collection

2.5.1 Aim1

Five to eight milliliter of blood was collected from each consenting participant following the in-person interview. Blood samples were collected in both EDTA (Ethylenediaminetetraacetic acid) Lavender cap tubes and whole blood red cap tubes and a laboratory identification number was assigned for each participant. The blood samples in EDTA tube were then separated into plasma,

red blood cells, and white blood cells, and then stored under -20 degrees Celsius at the county CDC. Biological samples from all study sites were then sent to the Jiangsu Provincial CDC, which was responsible for storing all samples at -70 degrees or colder for future tests. DNA samples were then extracted in the molecular epidemiology lab at the Department of Non-communicable Diseases (NCD) Prevention and Control at the Jiangsu Provincial CDC in Nanjing, China. Genotyping was performed at the UCLA Genotype and Sequencing Core, using a customized Fluidigm Dynamic 96.96 ArrayTM Assay (Fluidigm, South San Francisco, CA). Assays were based on allele-specific PCR SNP detection and Dynamic ArrayTM integrated fluidic circuits (IFCs). The SNP assay tagged allele-specific PCR primers and a common reverse primer. A universal probe set was used in every reaction, producing uniform fluorescence; furthermore, Fluidigm provided locus-specific primer sequences that allowed confirmation of target locations[92].

A total of 65 candidate SNPs were selected from tagSNPs regulating the pathways of microRNA, stem cell regulation, NF-κB, and HIF-1α. Table 2-1 showed the list of SNPs to be selected from. Each selected candidate SNP meets all these requirements: 1) the genotyping call rate is greater than 90% in this study population; 2) the minor allele frequency (MAF) in the Chinese-Han population is no less than 5%; 3) the distribution of the alleles is in the Hardy-Weinberg Equilibrium (HWE) among the controls in the study, with a Bonferroni adjusted significant level of *P*-value (0.00091 = 0.05/55).

2.5.2 Aim3

Samples were genotyped on the Illumina Human 610_Quadv1_B platform and Illumina Human 660W-Quad_v1_A platform. According to published materials online by FLCCA[148], quality

control (QC) on genotyping samples was performed and exclusion criteria were as follows: 1) samples with low completion rates; 2) samples with extreme mean heterozygosity rates. The thresholds were chosen based on the sample completion rates or sample mean heterozygosity distribution by each QC group; and 3) discordant expected duplicate samples. The average genotype concordance rate for the expected duplicates was great than 99.9%. QC on the subject level led to the following exclusions: 1) gender discordance; 2) subjects with Asian ancestry less than 86%; 3) subjects with first degree relatives in dataset; 4) subjects with incomplete phenotype, ever smoked, unknown histology or ineligibility. SNPs were excluded if Hardy-Weinberg equilibrium (HWE) *P*-value were smaller than 10^{-7} and or minor allele frequencies (MAF) were less than 0.01. The genotyping data of this GWA is available on the National Institute of Health (NIH) database dbGaP (study accession: phs000716.v1.p1). Phenotype data included in this database were age categories, case/control status, and histological types of cases. Information on the traits of interest in this study (age at menarche and age at menopause) was not collected in this GWA.

2.6 Statistical analysis

2.6.1 Aim 1

2.6.1.1 Descriptive data analysis and multivariable logistic regression

To provide description of the data, categorical variables were compared with χ^2 test while continuous variables with Student t-test. The Mantel trend test was used to assess if an ordinal categories of exposures exhibits a dose-response relationship with the outcome. Possible associations between menstrual, as well as reproductive history, and occurrence of lung cancer were tested with multivariable unconditional logistic regression models, adjusting for covariates.

According to a priori biological rationale [11, 54, 154], age, county of residence, BMI, exposure to tobacco smoking, family history of lung cancer, income, and education were adjusted for in the multivariable logistic regression models. Stratified analysis by smoking status was performed. Possible heterogeneity of the association of reproductive factors to the risk of lung cancer by smoking status has been tested with RERI and ROR. For never-smokers, age, county, and BMI were adjusted for. For ever-smokers, age, county, BMI, and pack-years of smoking will be adjusted for. ORs and 95% CIs were calculated for all the possible associations. Age, county, tobacco smoking, pack-years of smoking, and BMI were adjusted for in the logistic regression models for the genotyped sub-population. These covariates showed significantly different distributions between cases and controls in this sub-population. Tobacco smoking is always together with pack-years of smoking in the adjustment.

2.6.1.2 Semi-Bayes shrinkage

The genetic association of lung cancer was tested with unconditional logistic regression. Dominant, recessive or log additive genetic models are chosen according to the results. To correct the false positives arising from multiple comparisons and to address the sparse data issue, the semi-Bayes shrinkage method was applied using data augmentation[155]. Semi-Bayes shrinkage regresses the estimates towards a prior value to a degree proportional to their estimated variance. As a result, unstable estimates were pulled more and had more stringent rejection criteria than stable estimates. In this study, a null prior (OR=1, variance=0.5 and 95% CI=0.25,4.00) was assumed for the association between each SNP and the risk of lung cancer among the postmenopausal Chinese women[156, 157].

2.6.1.3 Genetic risk scores

The multigenetic index (MGI, number of risk genotypes from a set of observed SNPs) and polygenetic risk score (PRS, number of risk alleles from a set of observed SNPs) were calculated

to evaluate the genetic exposure in the aggregate. MGI was the sum of risk genotypes. If a genotype/two genotypes was protective for lung cancer, this genotype(s) was/were recoded as the reference level and the other genotype the index level[149]. PRS was calculated by weight of the log OR value in the adjusted logistic regression models based on log-additive genetic model. If the minor allele was preventive, the major allele was recoded as the index and the minor allele as the reference, i.e., the absolute number of risk alleles was recoded as 2- number of protective alleles. PRS and MGI were categorized into quartiles in this analysis [158, 159].

2.6.1.4 Effect modifications

The effect modification by tobacco smoking was calculated by relative excess risk due to interaction (RERI) for the additive scale and was by ratio of odds ratios (ROR) for the multiplicative scale. If the main effect or modifying variable showed protective effect (odds ratio point estimate<1), the reference level for this variable was redefined as the level with the lowest risk of lung cancer. In the analysis for genotyping data, all SNPs selected according to QC criteria were tested in the stratified analysis by high or low parity. Only SNPs tested statistically significant (according to the semi-Bayes estimates under any genetic model) in the main effect analysis or in the stratified analysis were tested for RERI and ROR. The genetic models were one of additive, dominant, or recessive. Covariates adjusted for in these models are the same with corresponding models for main effects (please refer to 4.1.4.1 Descriptive data analysis and multivariable logistic regression) [160].

2.6.1.5 Missing data processes

Complete case analysis was applied for all variables except pack-years of smoking and numbers of live birth and induced abortion in the calculation for crude, adjusted, semi-Bayes, RERI, and ROR estimates. The missing values in live birth and induced abortion were imputed by group-

specific median in the controls. (The missing rates of those variables with complete case analysis were all less than 10%.)

The miORs in this study was based on five rounds of multiple imputations using Markov chain Monte Carlo method (MCMC option in SAS version 9.4 proc mi), assuming multivariate normality of the data. The variables in the imputation were age, county, smoking status, pack-years of smoking, obesity, family history of lung cancer, candidate SNPs genotypes, and the effect modifying variable.

2.6.2 Aim 2

$\chi 2$ tests and Student t-tests were respectively performed for categorical and continuous variables to compare the cases with the controls in terms of distributions of the covariates. The Mantel trend test was applied to evaluate potential linear relationship between incremental categories of certain hormonal factors and probability of lung cancer occurrence. Unconditional multivariable logistic regression with fixed effects was applied to estimate the study-specific and combined odds ratios and 95% confidence intervals for hormonal factors. Forest plots were created and I_2 statistics were calculated to evaluate the heterogeneity between studies[161]. To account for the heterogeneity between studies, random effect was integrated for the analysis of the pooled dataset of all individual-level data. The mixed effect models were composed of a random intercept of study site to allow heterogeneity between study sites, and fixed slopes for exposure variables and covariates. Multinomial regression analyses were conducted to compare adenocarcinoma cases to controls, as well as squamous cell carcinoma cases to controls with hierarchical models that integrated random intercepts for study site. To explore the sources of heterogeneity, stratified analyses on smoking status and publication status were conducted. Age,

smoking status, CSI, and family history of lung cancer were adjusted for in the study-specific and pooled models according to a priori biological rationales[11, 35]. In addition, age at menarche was adjusted for in the analysis of age at menopause and age at first birth; length of reproductive window was adjusted for in the analysis of livebirth; age at first birth was adjusted for in the analysis of the first birth outcomes[1]. Complete case analyses were conducted. All *P*-values in this study were based on a two-sided α level of 0.05. SAS version 9.4, R version 3.5.2, and RStudio Version 1.1.423 were used for statistical analyses and visualization.

2.6.3 Aim 3

2.6.3.1 Selection of IV SNPs

Genetic instrumental variables were selected according to published primary GWAS studies and their summary statistics were extracted. These studies have to be published in English and searchable by PubMed. Up to February 8th, 2020, 627 and 238 SNPs were identified associated with age at menarche and age at menopause, respectively, in primary GWA studies[133-147], regardless of population ancestries, based on a *P*-value cutoff of 1×10^{-5}. The *P*-value cutoff was applied to the overall (initial GWA + replication) population. If a study did not report a combined *P*-value, the *P*-value and effect size from the largest sample size will be reported as long as the initial and replication samples each show an association of *P*-value < 1×10^{-5}. If a study did not include a replication stage, significant SNPs from the discovery stage will be reported. If a SNP was reported in more than one primary GWA studies, the study with the smallest *P*-value for this SNP will be used. Both regression coefficient (beta) and standard error (SE) were reported for 261 out of the 627 menarche SNPs and 126 out of the 238 menopause SNPs. The effect estimates for these SNPs are on continuous age scales. National Human Genome Research Institute- European Bioinformatics Institute (NHGRI-EBI) Catalog was used

to select potential IV SNPs. This database is currently mapped to Genome Assembly GRCh38.p13 and dbSNP Build 152.[162].

2.6.3.2 Two-sample Mendelian randomization

Statistical analysis were conducted by using R(version 3.6.2) and R studio (Version 1.2.5033). Unless specifically mentioned, statistical tests were two-sided with a significant level alpha set to 0.05. Tabulate evaluations were performed for phenotype (histology and age groups) distributions. Categorical age distribution was compared between cases and controls with Pearson's χ_2 test.

There are three major assumptions to be met for a Mendelian randomization study to test the null hypothesis that the exposure (E in Figure 1-3) does not cause the disease (D in Figure 1-3)[163]. Firstly, the genetic IV must be associated with the trait (E in Figure 1-3). *F*-statistics and *P*-values were used to evaluate the strength of the IV in this study.

Secondly, there must be no unmeasured confounders of the associations between genetic variants and outcome. Since genetic variants happen prior to all other variables, there is no measured/unmeasured/known/unknown variable (Z in Figure 3) that confounds the association between G and D, except population stratifications. The third MR assumption requires that the genetic variant could be associated with the outcome only via the exposure, i.e. there is no pleiotropy. MR-Egger regression approach was used in this study to assess the assumption of no pleiotropy[164]. In addition to test the null hypothesis, a fourth assumption of homogeneity of exposure effect on outcome should be met for the MR to provide accurate effect estimates[165]. Cochran's *Q* statistic and the corresponding *P*-value was used to evaluate the homogeneity

assumption. *Q* statistic, derived from the IVW estimate, follows a χ_2 distribution with degrees of freedom equal to the number of SNPs minus 1[166].

In the Step 1 of the two-sample summary-data MR, regression coefficients (Betas) and standard errors (SE)were obtained from literature[133-147]. For GWA studies using week and month as the unit, Betas and SEs were divided by 52.1429 and 12, respectively. For GWA studies estimating decreases in ages, regression coefficients and SEs were divided by -1. The harmonized Betas were explained as the increase in year (of age at menarche/menopause) per risk allele. The FLCCA Illumina reads were aligned to the complimentary DNA strand if the risk allele in Step 1 data happened to be on the other DNA strand (e.g. if FLCCA Illumina reads was "A" or "G" for rs1129700, and Step 1 risk allele for rs1129700 is "T", Illumina reads "A" was recoded to "T" and "G" was recoded to "C"). The risk alleles in Step 1 were set as the effect alleles in Step 2. In the Step 2 association modeling, the lung cancer status was regressed against the risk score, adjusted for age group. The risk score was the number of risk allele (0,1, or 2) and the missing information was imputed by mean in the control group. PRS were calculated and linked to lung cancer risk in order to avoid possible heterogeneity between IV SNPs in the two-sample method and to mitigate potential weak instrument drawbacks.

Inverse-variance weighted method and likelihood-based approach were applied to calculate the MR effect estimates as they both give similar estimates and precision to the two-stage least squares method for individual-level data, even when there are gene-gene interactions, as long as IV SNPs are not in linkage disequilibrium[121]. Weighted median approach was also used to calculate MR effect estimates because this approach is robust to pleiotropy even if up to 50% of

the SNPs are pleiotropic[167-169]. R package *MendelianRandomization* was used to calculate the effect estimates and 95% confidence intervals [170].

The formula of IVW method are shown below [121]:

$$\hat{\beta}_{IVW} = \frac{\sum_{i=1}^{g} X_g Y_g \sigma_{Y_g}{}^{-2}}{\sum_{i=1}^{g} X_g{}^2 \sigma_{Y_g}{}^{-2}},\ se(\hat{\beta}_{IVW}) = \sqrt{\frac{1}{\sum_{i=1}^{g} X_g{}^2 \sigma_{Y_g}{}^{-2}}}$$

an X_g is a β estimate of the association between each selected SNP and age at menarche (or menopause), a Y_g is a β estimate of the association between each selected SNP and lung cancer (from the FLCCA study), and a σ_{Y_g} is the standard error for the corresponding Y_g. ORs and 95% CIs were calculated using $\widehat{\beta}_{\mathrm{IVW}}$ and se($\widehat{\beta}_{\mathrm{IVW}}$). A β estimate in this calculation is the change in the log-odds of outcome per allele change of the SNP.

2.6.3.3 Sensitivity analysis

PRS were calculated as a sensitivity analysis to provide robust effect estimates given possible weak instrument effect and heterogeneity between IV SNPs in the two-sample method. The age at menarche PRS of the K$_{th}$ women is calculated as the sum of the number (or imputed doses) of risk-increasing alleles carried (G) of the n$_{th}$ SNP, weighted by the published regression coefficient (β_n) of the SNP-age at menarche association:

$$PRS_K = \sum_{n=1}^{45} \beta_n G_{Kn}$$

Similarly, the age at menopause PRS of the K$_{th}$ women is calculated as the sum of the number (or imputed doses) of risk-increasing alleles carried (G) of the n$_{th}$ SNP, weighted by the published regression coefficient (β_n) of the SNP-age at menopause association:

$PRS_K = \sum_{n=1}^{27} \beta_n G_{Kn}$

CHAPTER 3 Results

3.1 Menstrual/reproductive factors in association with lung cancer and modified by smoking status (Aim 1 Part 1)

3.1.1 Summary statistics

The average age in this post-menopausal female population was 67.21 years. Table 3-1 summarized the distribution of demographic and major risk factors. Cases and controls showed similar average ages and education/income distributions. Ganyu and Tongshan Counties contributed more lung cancer cases while Dafeng and Chuzhou counties contributed more controls. Significantly higher proportions of smokers and larger pack-years were observed in lung cancer cases than in controls. Cases were significantly more likely to be underweight and less likely to be overweight or obese than controls. Family history of lung cancer tended to happen among lung cancer cases rather than controls.

3.1.2 Menstrual Characteristics

According to Table 3-2, there was no significant statistics for the relationship between age at menarche and the odds of lung cancer in the entire study population. However, we found an 35% increased odds (Table 3-3) among never smoking subpopulation, comparing age at menarche between 16 and 17 years old with that <=15 years old (semi-Bayes adjusted odds ratio, sbOR=1.35, 95% CI=1.01, 1.80). The Mantel test *P*-value was 0.03, indicating a possible dose-response relationship. Compared with ages at menopause between 46 and 54 years, those later than 54 years old were associated with 1.61 times of odds of lung cancer occurrence in the whole study population (Table 3-2, sbOR=1.61, 95% CI=1.10, 2.36, Mantel test *P*-value=0.023). Age at menopause also showed 3% increased odds of lung cancer per one-year increase (sbOR=1.03,

95% CI=1.01-1.06). These aforementioned association for age at menopause seemed to exist among never smokers but could not be found in the ever-smoking subpopulation (Table 3-3). There was no evidence demonstrating an association between the length of reproductive window and the lung cancer.

3.1.3 Reproductive History

As shown in Table 3-2, increased parity is inversely associated with lung cancer. Women with 2-3 parity showed 30% and those with four or more showed 26% decreased odds in lung cancer occurrence, (parity=2 or 3: sbOR=0.70, 95% CI =0.53, 0.93, parity = 4 or more: sbOR= 0.74, 95% CI =0.55, 0.99, reference group is parity=1). The dose-response trend was not observed between increased parity per unit and lung cancer (P_{trend}=0.177 and the semi-Bayes confidence interval was across the null). When stratified by smoking status (ever and never) (Table 3-3), there seemed no obvious association between parity and the odds of lung cancer. A moderate gravidity was inversely associated with lung cancer (sbOR=0.71, 95% CI=0.53, 0.95, gravidity=2-3 compared with gravidity=0 or 1) in the study population (Table 3-2). Among never smokers, gravidity did not show a clear relationship with lung cancer. On the other hand, treated as a continuous variable, a one-unit increase in gravidity was significantly associated with 11% decrease in odds of lung cancer (sbOR=0.89, 95% CI=0.81, 0.99) for ever-smokers. A moderate number of live births was shown associated with 29% decreased odds of lung cancer in all the post-menopausal women (sbOR=0.71, 95% CI=0.43, 0.94, number of live birth=2-3 compared with 0-1). However, we did not observe meaningful association when stratified by smoking status in either ever- or never- smokers (Table 3-3).

Induced abortion, reported or not in Table 3-2 and Table3-3, did not show an associations with lung cancer. An increase of 13 ovulatory cycles (about one year) was related to 2% increase in the odds of lung cancer in post-menopausal women (sbOR=1.02, 95% CI=1.00+, 1.04) but it was not observed in subpopulations stratified by smoking status.

3.1.4 Exogenous Hormone Use

No obvious association was observed between OC use and lung cancer (Table 3-2 and Table 3-3).

3.1.5 Effect modification by smoking status

Assessment of potential interactions between menstrual and reproductive factors and smoking status on additive and multiplicative scales were performed. As reported in Table 3-4, gravidity at or below two showed an RERI of 1.71 with 95% CI of 0.33-3.38. The ROR of gravidity was 1.68 (95% CI=0.98, 2.89). These RERIs and RORs were suggesting superadditivity for the interaction between smoking and gravidity (Table 3-4).

3.2 SNPs in association with lung cancer and modified by parity (Aim 1 Part 2)

3.2.1 Summary statistics

In the entire Aim 1 study, there were 680 lung cancer cases and 1,808 controls, among which 191 cases and 564 controls were genotyped (Table 3-6). The participants with genotyping data were from Dafeng and Ganyu counties only. No sample from Chuzhou or Tongshan was genotyped. The average age in the controls of this genotyped population (67.34, standard deviation=8.53) was the same as the controls not genotyped. The education level seemed to be higher among controls who were not genotyped, however income levels seemed to be higher in the genotyped controls. The proportions of controls who smoked (35.46%), who have family history of lung cancer(3.72%), and who have BMI less than 18.5 (11.72%) were larger in the

genotyped population than the corresponding proportions in controls not selected to be genotyped (11.58%, 1.13%, and 7.19%, respectively), with *P*-values<0.001. In the genotyped population, controls showed a higher mean age (67.34) compared with cases (65.69). In Table 3-5, age, county, pack-year smoking, and BMI showed different distribution between cases and controls. Therefore, in the following multivariable analysis, these variables plus tobacco smoking status were considered as potential confounding factors and adjusted for in the data analysis, in order to increase precision for results.

3.2.2 Main effects of SNPs

There were 28 Micro RNA Related SNPs, 27 Stem Cell Related SNPs, 3 HIF-1α pathway, SNPs, and 7 NF-κB Pathway SNPs selected for this study. Among these 65 proposed candidate SNPs, there were 1 SNPs with MAF < 0.05, 9 SNPs with call rates <=90%, 2 SNPs not meeting HWE requirements and 2 with linkage disequilibrium (r_2 >0.8) with other SNPs. Therefore, in the final analysis, 51 SNPs were included. The SNP selection process was shown in Figure 3-1.

Table 3-8 showed the crude, adjusted, and semi-Bayes odds ratios for all 51 SNPs in all 755 participants, 367 participants with parity at or below 3 and 388 participants with parity at or above 4. Three microRNA-related SNPs showed significant association with lung cancer in this female Asian population. In all women, the minor allele G (compared with allele C) in rs2910164, a tagSNP for pre-miR-1046a (a microRNA gene), showed 59% increased lung cancer odds under recessive model. This association remained in people with parity at or above 4 and did not exist among people with parity at or below 3. The C allele (compared with T) in rs197412 showed a reverse association with lung cancer (sbOR=0.54, 95% CI=0.32, 0.90),

compared with allele T, under dominant model, among people with higher parity (>=4) only. This SNP marks Gemin3, a gene involved in microRNA processing and maturation. The minor allele G (compared with allele T) in rs2953 was associated with 77% higher odds of lung cancer (95% CI=1.01, 3.12) under recessive model. This effect was seen in the entire genotyped population and was not seen in any sub-population defined by parity. Rs2953 is a tagSNP for CTNNB1 gene, which encodes an up-regulator of Wnt signaling pathway and is targeted by microRNA-589.

Two SNPs related to stem cell pathway showed associations with lung cancer(Table 3-7). The minor allele T (compared with allele C) in rs1126497 has shown 87% increased odds of lung cancer (95% CI=1.29, 2.72) in all genotyped samples under dominant model. This association was stronger among women with lower parity (<=3), showing 105% increase in the odds of lung cancer (95% CI=1.22, 3.43), but was not obvious among women with higher parity. Rs1126497 in the EpCAM gene functions in epithelial to mesenchymal transition. Rs3734637 (HEY2 gene in Notch signaling) showed 33% decreased odds of lung cancer (minor allele C compared with allele A) with a 95% CI of (0.47, 0.98) under dominant model in the entire genotyped population.

Two SNPs in NF-κB Pathway were associated with lung cancer (Table 3-7). The minor allele C (compares with allele A) in Rs2230793, a SNP in IKBKAP gene, was associated with 32% decreased odds of lung cancer (95% CI=0.47, 0.97) under dominant model in all genotyped population. This effect was stronger (sbOR=0.58, 95%CI=0.35, 0.93) among women with lower parity and was not observed among women with higher parity. The other SNP, rs12894467

showed 63% increased odds of lung cancer associated with minor allele C (compared with allele T) with a 95% CI of (1.13, 2.35) under dominant model among the entire population. This SNP is a tagSNP for the miR-300 gene.

3.2.3 Main effects of menstrual and reproductive factors

In this population with genotyping data, there was no evidence of overall association between menstrual and reproductive factors, probably because of small sample size (Table 3-9). The only association observed was for the times of abortions, which showed an OR of 7.06, with a 95% CI of (1.50 , 33.30) for participants with 3 or more induced abortions, compared to those with no abortion (not shown in the Table 3-9). However, this large odds ratio and wide confidence interval could be due to the sample size. There were only 8 people who reported 3 or more abortions (4 cases and 4 controls) in this population. Since parity was associated with lung cancer in the entire Aim 1 study population (with 680 cases and 1,808 controls), the effect modification by parity was evaluated in this genotyped sub-population.

3.2.4 Effect modification by parity on the association between SNPs and the odds of lung cancer

In Table 3-11, the estimated RERIs and RORs for the seven SNPs (please refer to 3.2.2 Main effects of SNPs) suggested a sub-additive and sub-multiplicative effect modification by lower parity(<=3) in the association between rs197412 (TT genotype), a microRNA-related gene, and the occurrence of lung cancer.

3.3 Association between hormonal factors and lung cancer in Asian women: a pooled analysis from the International Lung Cancer Consortium (Aim 2)

3.3.1 Summary statistics

Among a total of 2,456 lung cancer cases and 5,342 controls (Table 3-12) in this pooled analysis, 86.80% of cases and 87.82% of controls were post-menopausal, as shown in Table 3-13. Four out of six studies (GEL1, Aichi, MEC, and SCHS) provided histologic information. Among them, more than half (54.44%) of non-small cell carcinoma of the lung were adenocarcinoma, and 7.03% were classified as small cell lung carcinoma. Other major subtypes of non-small cell carcinoma of the lung included squamous cell carcinoma (12.13%) and large cell lung carcinoma (5.10%). Table 3-14 summarized the distributions of covariates. The average ages were 66.46 in cases and 66.54 in control, the majority of the study participants (62.26% cases and 70.73% controls) had elementary or lower education. The country with largest proportion of participants was China (49.02% cases and 53.48% controls), followed by Singapore (21.50% cases and 21.56% controls), United States (20.32% cases and 18.68%), and Japan (7.53% cases and 3.46% controls). In this female study population, most participants (65.31% cases and 83.81% controls) never smoked; 10.50% cases and 6.46% controls used to be smokers; 23.74% cases and 9.27% controls were current smokers. 1.55% cases and 9.06% controls had first-degree relatives diagnosed with lung cancer. The distributions of education, country of origin, smoking status, CSI, pack-year, family history of lung cancer appeared to be different between cases and controls.

3.3.2 Study-specific estimates

In the study-specific analysis of childbirth (Figure 3-2 middle panel forest plot), none of individual or combined studies showed evident associations, with the summary odds ratio as 0.86

and a 95% CI of (0.68, 1.07). The I_2 statistic was 50.25% for childbirth, showing substantial heterogeneity between individual studies. The forest plot for menopausal status (Figure 3-2 upper panel forest plot) described a negligible heterogeneity between the five eligible studies and reported a summary odds ratio of 1.07 (95% CI=0.89, 1.28). OC use (Figure 3-2 lower panel forest plot) showed a consistent protective association in individual studies and in the pooled dataset (summary OR=0.73, 95% CI=0.61, 0.86). The I_2 statistic (64.49%) implied a considerable amount of heterogeneity.

3.3.3 Pooled analysis results

Table 3-15 and Table 3-16 showed the results from the pooled analysis with mixed effect models in the entire population as a whole and by histological types, respectively. Menarcheal ages at 15-16 and 17 or later seemed to present 16% (95%CI=1.01, 1.33) and 24% (95%CI=1.05, 1.45) higher odds of getting lung cancer, compared with menarcheal ages at or below 14 (P_{trend}=0.008). Each one-year increase in age at menarche might be associated with 4% higher odds of lung cancer (95% CI=1.01, 1.07). Similar trend of age at menarche was observed for adenocarcinoma but not for squamous cell carcinoma (Table 3-16). A late menopause (55 years or older) was associated with 24% increased odds in lung cancer occurrence (95% CI=1.02, 1.51), given <=49 years was taken as the reference group (Table 3-15). Menopausal age did not seem to amend likelihood of having either adenocarcinoma nor squamous cell carcinoma (Table 3-16). We also discovered a 39% higher odds (95% CI=1.13, 1.71) of having lung cancer in people with non-natural menopause, compared to people with natural menopause (Table 3-15). This association was also observed for adenocarcinoma but not for squamous cell carcinoma (Table 3-16). In the entire study population composed of six studies, a greater length of reproductive window did not manifest a sign of higher or lower probability of diagnosed lung

cancer, although in the stratified analysis by histology (GEL1, Aichi, MEC, and SCHS only), a longer (>=36 and <50 years) reproductive window seemed to be at declined probability of diagnosed adenocarcinoma (OR=0.71, 95% CI=0.56, 0.89, and P_{trend}=0.003). As a continuous variable, each one more year of reproductive window was associated with 2% lower probability of diagnosed lung cancer (OR=0.98, 95%CI=0.96, 0.99). These patterns were not observed for squamous cell carcinoma.

With respect to childbearing history, according to Table 3-15, 3 to 4 live births entailed 18% lower probability of being diagnosed with lung cancer (OR=0.82, 95% CI=0.72, 0.94) than 0 to 2 live births; 5 or more births entailed 29% lower odds of diagnosis (OR=0.71, 95% CI=0.60, 0.84). Trend test (*P*-value<0.001) corroborated that higher categories of live birth were associated with reduced possibility of being diagnosed with lung cancer to a larger extent. Every live birth might be related to 6% lower possibility of being diagnosed with lung cancer (OR=0.94, 95% CI=0.91, 0.97). Women who experienced their first deliveries at an older age were more likely to have developed lung cancer (OR=1.23, 95% CI=1.06, 1.43 for 21 to 25 years old; OR=1.27, 95% CI=1.06, 1.51 for 26 years or older), compared with people whose first deliveries were prior to 20 years old (*P*-value of the trend test=0.010). Similar patterns were prominent for adenocarcinoma but not for squamous cell carcinoma (Table 3-15).

In table 3-15, former OC use was associated with 35% decreased odds of being diagnosed lung cancer cases (OR=0.65, 95% CI=0.49, 0.85), while current use associated with 26% decreased possibility of lung cancer (OR=0.74, 95% CI=0.57, 0.96). Each additional year of use implied 3% decrease in the probability of diagnosed lung cancer (OR=0.97, 95% CI=0.95, 1.00-). There was no clear association between estrogen use (in HRT) and lung cancer in this

study. Inverse association of OC use was found for adenocarcinoma but not for squamous cell carcinoma (Table 3-16).

3.3.4 Analysis of sources of heterogeneity

Table 3-16 analyzed possibly heterogeneity by publication status in the association between hormonal factors and lung cancer. Three of the six participating studies have been published previously[1, 59, 171]. In the current pooled analysis, the positive association between menopause and odds of lung cancer were detected in the published studies but no in the unpublished studies. In the published studies, both older ages at menarche and menopause seemed related to increased possibility of lung cancer. On the other side, in unpublished studies, older ages at only menarche seemed to be associated with higher possibility, while older age at menopause seemed to have an inverse association. Childbearing histories probably embodied less heterogeneity, with more live births showing fewer past lung cancer diagnoses, and later age at first delivery showing the opposite, in both published and unpublished studies. A considerable heterogeneity of exogenous hormone use might exist as OC entailed 39% lower probability of previous lung cancer diagnosis (95% CI=0.47, 0.80), at an annual rate of 6% (95% CI=0.90, 9.98) in published studies, while no significant results were found in unpublished ones. The stratified analysis on smoking status showed no statistical effect modification for menstrual characteristics, childbearing histories, and oral contraceptives use. According to Table 3-18, estrogen use in HRT might be a related to reduced lung cancer probability among Asian women who never smoked.

3.4 The role of age at menarche and age at menopause in lung cancer: a Mendelian randomization study (Aim 3)

3.4.1 Summary statistics

The criteria and process of IV SNPs selection were summarized in Figure 3-3 and Figure 3-4. The linkage disequilibrium between selected SNPs for menarche and menopause MR studies were shown in Figure 3-5 and Figure 3-6. As shown in Figure 3-3, for age at menarche, among the 261 SNPs selected from published primary GWA studies, 52 SNPs were found in the FLCCA dbGaP SNP profile. Tested in this population, 5 out of the 52 SNPs showed genotyping call rates less than 95%; 4 showed MAF less than 0.01; and 1 was tested deviated from HWE (specified as having a *P*-value smaller than 0.05/n). R squared (r_2) statistic was calculated to test LD. For the three SNPs in LD (specified as having r_2>0.05 between each two), the two with the smallest *P*-value was maintained (Figure 3). This clumping procedure minimize the correlation between selected IV SNPs and at the mean time preserve the strongest statistical evidence[172]. These selection processes left 40 SNPs as IV in the two-sample MR and PRS based analysis for age at menarche.

Shown in Figure 2, there were 238 SNPs reported in association with age at menopause according to published primary GWA studies. Beta and SE were reported for 126 of them, among which 31 overlapped with FLCCA dbGaP SNP profile. In these 31 SNPs, 2 were excluded in this study because their genotyping call rates were lower than 95%. There were 3 SNPs excluded due to a MAF less than 0.01, 1 SNP excluded due to deviation from HWE, and 1 SNP was removed in the clumping procedure (Figure 4). In the end, 24 IV SNPs were selected in the two-sample MR and PRS-based analysis for age at menopause.

The summaries of SNPs used as IV was in Table 3-19 and Table 3-20 . There were 40 IV SNPs in the MR for age at menarche and 24 IV SNPs in the MR for age at menopause. Because only SNPs with first step *P*-values less than 10^{-5} and without linkage disequilibrium were selected as IVs, the overall *F*-statistics for age at menarche SNPs and age at menopause SNPs were both larger than 20, maintaining a bias of the IV estimator less than $1/F$= 5% of the bias of the observational estimator. The MR-Egger intercept was estimated to be 0.008(95% CI=-0.014, 0.031, *P*-value=0.460) for age ate menarche and -0.006(-0.035, 0.024, *P*-value=0.695). The Cochrane *Q* statistic for age at menarche was 53.2859 on 39 degrees of freedom (*P*-value = 0.0633). The *Q* statistic for age at menopause was 30.6973 on 23 degrees of freedom, (*P*-value = 0.1304).

Table 3-21 summarized the phenotype information in FLCCA. In the 4,922 diagnosed lung cancer cases, 3,595 (73%) had adenocarcinoma, 660 (13.4%) had squamous cell carcinoma and 667 (13.6%) had other histological subtypes. In the 4,922 cases and 3,959 controls, more than half aged between 50 and 70. The age distribution in the cases seemed to be older than in the controls (χ^2 test *P*-value was less than 0.001).

3.4.2 MR estimates and stratified analysis

The graphic presentation of the relationship between SNP-exposure associations and SNP-outcome associations were depicted in Figures 3-7, 3-8, 3-9, and 3-10. The scatterplots appeared to describe increased lung cancer odds correlated with older menarcheal and menopausal ages. The effects of age at menarche and menopause estimated by multiple MR methods and PRS-based analysis were presented in Table 3-22. For age at menarche, the IVW method resulted in

1.03 times of odds of lung cancer in people whose age at menarche is one year older, with 95% CI=0.87, 1.21. There were no remarkable effect estimates for age at menarche using IVW methods (OR=1.02, 95% CI=0.87, 1.21). The point estimates and confidence intervals for both traits using maximum likelihood method are almost the same as using IVW method. There were no evident association for age at menarche or menopause using any of the two-sample MR methods (including IVW, maximum likelihood, weighted median-based, and MR-Egger methods).

3.4.3 Sensitivity analysis

As shown in Table 3-22, increased PRS per unit showed 3% increased odds (95% CI=0.89, 1.19) of lung cancer for every one unit increase in PRS. The odds ratio and 95% CI for age at menopause in the PRS-based analysis was 1.02(0.96, 1.09). The stratified analysis for adenocarcinoma and squamous cell carcinoma showed no notable association between age at menarche or menopause and lung cancer.

CHAPTER 4 Discussion

4.1 Menstrual/reproductive factors in association with lung cancer and modified by smoking status (Aim 1 Part 1)

In the present analysis of hormonal/reproductive factors, after controlling for potential confounders and correction using semi-Bayes shrinkage, later age at menopause was found to be associated with increased odds of lung cancer. This relationship was apparent in the never-smoking subpopulation, but disappeared in the ever-smoking subpopulation. A higher parity,

gravidity, and number of live births were associated with reduced odds of lung cancer, respectively. Increased number of ovulatory cycles appeared to be associated with increased susceptibility of lung cancer. Other hormonal factors such as reproductive window, number of abortions, and outcomes of first pregnancy were not obviously associated with lung cancer in this study population.

The stratified analyses for never- and ever-smokers indicated that reproductive factors might interact with smoking status in the development of lung cancer. Superadditivity was corroborated by RERIs, showing a considerably greater joint effect of smoking and low gravidity than expected under an additive model without interactions.

Between 1/1/1988 and 6/19/2020, there were more than 20 epidemiologic studies [48-50, 53-56, 58] that tested for associations between hormonal factors and risk of lung cancer. A meta-analysis [50] showed a statistically significant decreased risk of lung cancer in women with late age at menarche. However, this result was only within studies in North America, where Caucasians predominates. Because the effect of hormonal factors on lung cancer might vary by race/ethnicity, inverse association was observed in the current JFC Study. An age at menarche greater than 18 years old could be a marker of poor childhood nutritional status, which has long-term adverse influence on health [56, 173, 174].

A greater menopausal age was hypothesized to increase the risk of lung cancer since a greater menopausal age means more exposure to estrogen[175, 176]. However, an ILCCO pooled analysis [48] with a mixed racial groups did not observe a meaningful association. A cohort

study of Asians (Singapore, SBCSP) [56] showed a null association without adjusting for smoking intensity or pack-years of smoking, leaving potential residual confounding by smoking. In this present JFC Study, where missing information was minimal and pack-years of smoking was adjusted, increased odds of lung cancer by greater age at menopause was detected. This finding was consistent with three other studies among Chinese women [54, 55, 58].

In this present study, higher parity, gravidity, and live births were associated with decreased odds of lung cancer, which is consistent with all other Asian studies[54-56]. Parity and gravidity take into consideration the effect by miscarriage, abortion, stillbirth, and live birth, which results in an estrogen surge and accumulation for a period of time and reduce the number of ovulatory cycles. Our study was the first to report that an increased odds of lung cancer was associated with increased number of ovulatory cycles, supporting the hypothesis that regular dynamics of estrogen during normal ovulatory cycles, rather than accumulative endogenous or exogenous estrogen exposure, might increase the risk of lung cancer.

It has long been believed that there are potential interactions or effect modifications between tobacco smoking and other risk factors on the development of lung cancer. [37, 177]. This JFC study with post-menopausal women is the first study to report the effect modification by smoking, showing that the risk smoking added to those with fewer pregnancies was greater than that added to those with more pregnancies.

Estrogen is thought to have an effect on lung cancer via estrogen receptors (ERs). Estrogen receptors α and β (ERα and ERβ), the two major types of ERs, are found in bronchial and

alveolar epithelia and airway smooth muscle[16]. Both ERα and ERβ are ligand-activating transcription factors activated by 17-β estradiol (E2), the activation form of estrogen in human. The binding of E2 to ERs leads to dimerization and nuclear translocation of theses ERs. In the nucleus, ligand-bound ERα/ERβ dimers bind to the estrogen response elements (ERE) in the promoters of target genes to control cell proliferation, differentiation and apoptosis. ERs also associates with and activates EGFR (epidermal growth factor receptor, a receptor tyrosine kinase) thus triggering MAPK/ERK (mitogen-activated protein kinases/extracellular signal-regulated kinases) pathway and up/down regulating the transcription of genes that promote proliferation and invasion of lung cancer cells [15].

Strengths of this current study included homogeneity in terms of race/ethnicity, a population-based study design, a large sample size, and a large proportion of non-smokers, which are important to reduce bias. The weak effect of menstrual and reproductive factors on lung cancer could be undetectable in a population dominated by smokers because of the strong association between smoking and lung cancer [54]. This study design also minimized possible selection bias by having population-based controls instead of hospital-based designs and by having very low missing rates of exposure variables of interest. In previous studies of the same topics, multiple menstrual and reproductive factors have been tested at the same time within one analysis, possibly resulting in false positive findings from multiple comparisons without correction. In our study, semi-Bayes shrinkage approach was applied to mitigate potential false positivity by updating independent null priors for regression coefficients with observed data[178]. Semi-Bayes estimates were calculated also to improve the sparse data problem [155].

The weaknesses of this study included a lack of histologic categorization of lung cancer patients. Secondly, there could be recall biases brought by the case-control study design. However, all lung cancer cases were diagnosed within one year of interview. In addition, the study was not initially designed to test the association between hormonal factors and lung cancer and the participants were never told the hypothesis. Therefore, their recalls for their previous exposure information were relatively objective representing their usual life before the diagnosis of lung cancer and the recall bias should be minimum. Lastly, the sample size in the assessment of interaction was relatively small so that we were unable to verify the causal interactions between smoking status and those menstrual and reproductive factors.

4.2 SNPs in association with lung cancer and modified by parity (Aim 1 Part 2)

This current study evaluated the main effects of SNPs among postmenopausal Asian women and the effect modification by parity. The results showed that 7 SNPs were associated with lung cancer in this population, among which the effect of one SNP was modified by parity. This suggested that genes involved in microRNA, cancer stem cell, and NFkB pathways could possible increase or decrease the risk of lung cancer and some of these effects might be modified by parity.

This current study is the first to observe associations between lung cancer susceptible genes and lung cancer among postmenopausal Asian women. However, the relatively small sample size remains a limitation for evaluation of effect modification.

A few single nucleotide polymorphisms (SNPs) of Kras-related *let-7*[179], *miR-195a2*[180, 181], and *RAN*[72] genes have been identified to be associated with risk of lung cancer. Non-

smoking minor allele carriers (CT+TT vs. CC) of *RAN* rs14035 had higher odds of lung cancer (posterior aOR=1.28, 95% posterior limits=1.00, 1.63) in the LA Study[73]. However, the minor allele did not predict the development of lung cancer among non-smokers in the pooled Jiangsu+Taiyuan study[72]. The latter study also detected a decreased risk among individuals with the CT genotype compared to CC type among Chinese non-smokers exposed to ETS. All of these studies adjusted for sex and did not examine whether the associations are differ by sex. In this current study of postmenopausal Asian women, SNPs in the pre-miR-1046a, Gemin3, and CTNNB1 genes showed statistically significant association with the risk of lung cancer. The C allele (compared with T) in rs197412 (Gemin3 gene) showed protective effect against lung cancer (sbOR=0.54, 95% CI=0.32, 0.90), compared with allele T, under dominant model, among people with higher parity (>=4) only, the RERI and ROR suggested that a microRNA-related gene such as Gemin3 and a lower parity could possibly jointly increase the susceptibility of lung cancer. It has been hypothesized that elevated levels of estrogens and their metabolites inside the lungs can cause widespread repression of microRNA and contribute to lung tumor development[182].

Two Stem Cell Related SNPs and two NF-κB Pathway-related SNPs were associated with the risk of lung cancer (Table 3-7). However, no obvious effect modification by parity was detected in this study population. Cancer stem cells (CSCs) were believed to be responsible for cancer metastasis and relapse as a group of cancer cells which renew themselves and persist. NF-κB and HIF-1α are both transcription factors that regulate cell proliferation and survival.

4.3 Association between hormonal factors and lung cancer in Asian women: a pooled analysis from the International Lung Cancer Consortium (Aim 2)

This ILCCO pooled analysis of six Asian studies was the first and largest comprehensive investigation on the association between hormonal/reproductive factors and lung cancer among Asian women. It showed in Asian women, later age at menarche (17 years+), older menopausal ages (55 years+), and non-natural menopause were associated with greater likelihood of getting lung cancer. In this study population, increased times and earlier experience of childbirth were associated with decreased probability of being diagnosed with lung cancer. We also observed a reduced likelihood of being diagnosed with lung cancer among oral contraceptives users. The longer time of OC use, the smaller chances of lung cancer among Asian women. The pooling analyses allowed heterogeneity among studies (possibly derived from different publication status), adjusted for potential confounders (age, smoking status, comprehensive smoking index, and family history of lung cancer), and reflected more of adenocarcinoma than squamous cell carcinoma because of Asian women.

The associations between hormonal factors and lung cancer in observational epidemiological study were explained by the potential biological and etiological mechanisms of estrogen and estrogen receptors in lung cancer development. Estrogen receptors α and β (ERα and ERβ), the two major types of ERs, were found in NSCLC cell line, and normal and cancerous lung tissue[16, 183, 184]. Estrogen receptors either translocate into the nucleus and function as transcription factors, or are associated with EGFR and trigger downstream biochemical signaling cascades such as MAPK/ERK (mitogen-activated protein kinases/extracellular signal-regulated kinases) pathway to regulate cell proliferation and invasion, leading to the development of lung

cancer.[15]. Lung cancer patients with higher expression of ERβ, aromatase, and the two combined, were observed to have a lower survival rate[185, 186]. Timings of menarche, menopause, the number of pregnancies, and the use of OC/HRT represent the cumulative exposure to estrogen in one's life, which might play some role in the development of lung cancer.

This study is the only endeavor to pool individual-level data on this topic for Asian populations. Our analysis discovered an increased lung cancer probability in relation to older age at menarche, which could not be found in other Asian [54, 55, 58, 61, 64, 187] and Caucasian studies. According to a meta-analysis which observed older age at menarche related to reduced risk of lung cancer in North American women (RR, risk ratio=0.83, 95%CI=0.73, 0.94) [50], it seemed age at menarche stands for different effects in lung cancer occurrence between Asian and Caucasian populations. Our analysis corroborated the association between older age at menopause and elevated probability of lung cancer found in other Asian studies[54, 55, 58, 64] and elaborated it with subgroup analyses of histologic types and publication status. For adenocarcinoma, a longer reproductive window was associated with a weaker tendency of getting lung cancer. This pattern was consistent with the fact that later menarche associated with increased lung cancer probability and age at menopause did not show a lucid relation, according to Table 3-16. Publication status did contribute to the heterogeneity (I_2=50.25% in Figure 3-2) in the study of menstrual characteristics. In published studies, probability of lung cancer diagnosis was associated with both older age at menarche and older age at menopause, their effects probably canceled out and resulted in non-significant statistical estimates of reproductive window(Table 3-17). In unpublished studies on the other hand, late age of menarche was associated with raised probability of lung cancer occurrence while older menopausal age showed

a decreasing pattern (however not significant, probably due to small sample size) of lung cancer emergence, resulting in a longer reproductive window associated with significantly reduced probability of being diagnosed with lung cancer (Table 3-17).

In our analysis, more live births and earlier first delivery explicitly protected women from lung cancer. These associations were mainly reflected in adenocarcinoma, and in published studies, and were however not found in unpublished studies or for squamous cell carcinoma. In published studies composed of mainly European descendants, the associations regarding livebirth were the opposite to our study and the effect of age at first birth was not detected[188]. Seow et al. [187] reported in Singaporean among female non-smokers, three or more livebirths were associated with decreased probability of adenocarcinoma diagnosis (OR=0.57, 95% CI=0.37-0.89) but not squamous cell carcinoma. In 2013, Gallagher et al. [55] found in the Shanghai female textile workers' study, a 30% lower risk of lung cancer in those with 5 or more live births, but no clear association was identified between number of pregnancies and lung cancer. These statistics supported the hypothesis that more ovulations and menstrual cycles are related to higher risk of lung cancer[1] as there is no ovulation during pregnancy and live birth entails the longest duration of pregnancies (longer than abortion and miscarriage). Lim et al. found in Chinese women in Singapore, there was a 92% higher odds of lung cancer (95% CI=1.37-2.69) in women who delivered their first babies at an age between 26 and 30, compared with people whose first delivery was at 20 years old or younger. This result is consistent with our ILCCO pooling analysis of Asian women. Other studies of Asian women and other female populations did not report the observed association between age at the first birth and lung cancer or they reported reverse associations as in the article by He et al. in 2017. In this case-control study of Chinese

women, giving first birth at or after 25 years old showed decreased odds, compared with giving first birth before 25 years old (OR=0.51, 95% CI=0.38, 0.69)[58].

With respect to exogenous hormone use, our study showed reduced lung cancer odds among OC users, consistent with the ILCCO pooled analysis composed of studies in North America and Europe[49]. Nevertheless, a case-control study in China found increased odds of lung cancer among people with OC use (OR=1.84, 95% CI= 1.11, 3.06). In this study, age, body mass index, education, occupation, marital status, tobacco smoking, passive smoking, alcohol drinking, cooking oil fume, tea consumption, lung diseases history, and family history of cancer were adjusted for[58].

There were a couple of weaknesses in this study. Firstly, the definition of non-smokers was different between studies. The maximum number of cigarette consumption in a non-smoker's life was 365 in GEL1, 20 packs in MEC, and 100 in JFC, NJLCS, and SCHS. Aichi study defined non-smokers as those who never smoked. In our statistical models, both smoking status (never, former, or current) and CSI (absolute value) were included in order to improve the accuracy. Because body mass index, second-hand smoking, occupational exposures, and EGFR mutation status were not available in all six studies, these variables were not able to be adjusted for or studied. In the published Aichi study[171], ages at menarche between 14 and 15 and the largest tertile of reproductive window length showed prominent effects on EGFR-mutated lung cancer, which did not exist among females with wild-type EGFR genes. In the future, EGFR-mutated lung cancer could be further studied among available ILCCO studies, not limited to studies included in current analysis.

There were several strengths of this study as well. Firstly, by pooling six studies, we had a large sample size for a less studied population, which entitled us with great precision and statistical power and better feasibility of subgroup analyses. Although age at menarche was studied in every Asian study on lung cancer, our study was the only one with a strong association. These estimates remained consistently significant among both smokers and non-smokers, in published and unpublished studies, and for adenocarcinoma. Secondly, in this study, based on individual-level data, exposure variables and covariables were collected and harmonized. Pooling studies overcome difficulties in the meta-analyses, which summarize published study results without using individual-level data. Unharmonized exposure measurement (for example, different categorizations of menarcheal/menopausal ages, and choices between parity, gravidity, and live birth to be counted in different studies) in each study was a major barriers for pooling study when variables have to be combined, harmonized, and analyzed. Our pooled study unified exposure measurement and focused on Asian populations. As uniformed categorization standards were used, dose-response effects could be evaluated. Thirdly, for an etiological research on lung cancer, it was very important that smoking-related information were collected in much details over all of the participating studies. Smoking intensity (number of cigarettes per day), duration of smoking (years), and time since smoking cessation (years) were all available in 6 studies and were integrated into CSI. Although residual confounding could never be completely eliminated, CSI assessed cumulative exposure to tobacco smoking and worked well in lung cancer studies[153, 189]. Last but foremost, large sample size and detailed information collection enabled the investigation on the source of heterogeneity, which is a crucial concern in any pooled analysis. Study-specific analyses and subgroup analyses were performed. Study-specific analyses

identified no specific difference between case-control and nested case-controls studies (Figure 1). They nevertheless showed moderate to substantial heterogeneity. Therefore, mixed effect models with random intercepts of study site were applied to allow heterogeneity among studies thus improving the accuracy of results. Mixed effect models themselves did not evaluate the source of heterogeneity, therefore, subgroup analyses were performed for smoking status and publication status. The results remained almost identical between smokers and non-smokers, in terms of menstrual characteristics, childbearing histories, and OC use (Table 3-18). However, whether a study was previously published or not did contribute to the study heterogeneity. Published studies seemed to have more statistically significant results and these evident results were mainly for more frequently studied hormonal factors (Table 3-17). By pooling individual-level data from all eligible ILCCO studies, stronger association was observed for both frequently- and less- studied hormonal factors.

4.3 The role of age at menarche and age at menopause in lung cancer: a Mendelian randomization study (Aim 3)

In light of inconsistent results from observational epidemiologic studies, this research aimed at exploring the causal relation between ages at menarche and menopause and the risk of lung cancer among Asian women. The two-sample MR and PRS-based analyses using GWA data found no evidence of causal effects of age at menarche and age at menopause on lung cancer occurrence, most likely due to limited power of the study.

Multiple published observational studies [48, 49, 53-56] observed no evident results for the association between age at menarche and the risk of lung cancer among Caucasian and Asian populations. A meta-analysis found older age at menarche related to reduced risk of lung cancer

in North American women (RR=0.83, 95%CI=0.73, 0.94) [50]. An older age at menopause appeared to be associated with 22% elevated risk of lung cancer in a cohort study among Asian women in Shanghai, China (49-51 vs <=48 years old: HR=1.22, 95%CI=1.03, 1.46). Similar results have been found in three case-control studies in China[1] (>54 vs <46 years old: OR= 1.61, 95% CI=1.10, 2.36), Singapore [54] (>=52 vs <=48 years old: OR=1.34, 95% CI=1.03, 1.74) plus the Aim 1 study of this dissertation. The Aim 2 pooled analysis on Asian populations also found the similar results for age at menopause for Asian women. Nevertheless, a cohort study in Singapore showed no statistically significant results[56]. In studies on Caucasian population, an older ages seems to be either increasing, decreasing, or not changing the risk of lung cancer[48-50, 53].

MR studies can be considered similar to a randomized controlled trial in that genetic variant is assigned randomly at conception. MR estimates are therefore not affected by classical confounding factors which were adjusted for or were not measured in the traditional observational studies[169]. MR estimates are valid under the three MR assumptions. Weak instrument, if exists, is the violation of the first MR assumption. In the two stage least squares (2SLS) approach, the strength of G-E associations are usually measured by *F*-statistic[190], the ratio of the mean square of the model to the mean square of the error, and can be expressed as a function of the first-stage R^2, the sample size (n) and the number of IVs(K):

In two-sample approach where summarized data are used, R^2 in the first sample could not be calculated. However, in this study, each IV SNP in the first-step GWA were independent (with LD $r^2<0.05$ and located in a different chromosome region) and showed a *P*-value smaller than

1.0 x 10^{-5}, corresponding to a *F*-statistic larger than 20[121]. Therefore, the *F*-statistic in the first step in this study is at least 20. The "rule of thumb" *F*-statistic is as least 10, to maintain a bias of the IV estimator less than 1/*F*= 10% of the bias of the observational estimator[191, 192]. Therefore, the weak instrument bias in this study should be minimal. The third MR assumption of no horizontal pleiotropy was evaluated with MR-Egger method. MR-Egger relies on the Instrument Strength Independent of Direct Effect (InSIDE) assumption, which assumes that the pleiotropic effect is not mediated via the risk factor of interest[164]. In MR-Egger method, the pleiotropic effect is evaluated by regressing the genetic variants' effect on the outcome against the genetic variants' effect on the trait and an intercept. In cases where the intercept is zero, InSIDE assumption is satisfied, indicating pleiotropic effect either does not exist or is balanced thus not detected. In this study, both the intercepts of MR-Egger regressions for age at menarche and age at menopause were not different than zero (age at menarche: 0.008, 95% CI=-0.014, 0.031, *P*-value=0.460; age at menopause: -0.006, 95% CI=-0.035, 0.024, *P*-value=0.695). Therefore, this study is showing no detectable pleiotropy, although residual pleiotropy is difficult to exclude. Residual pleiotropy is a general limitation of MR, especially when exploring complex traits such as age at menarche and age at menopause[168]. In this study, weighted median estimator was applied to obtain robust effect estimates regardless of certain amount of pleiotropy. This estimator is the median of a distribution of Wald ratio estimates, thus less sensitive to the pleiotropic IV SNPs. This estimator is robust against a maximum of 50% of pleiotropic SNPs[167-169].

To test the fourth MR assumption regarding homogeneity, Cochran's *Q* statistic was calculated. Even though the results from this study showed no significant heterogeneity according to the *Q*

statistic and associated *P*-values, we have used PRS-based analysis to acquire robust estimates in the existence of possible heterogeneity and weak instrument effect. In addition to the aforementioned facts, there are some additional strengths in this study. There are restrict QC steps in this study. Genotyping call rate, HWE, MAF, and LD r_2 were all considered to select IV SNPs. Individual-level raw data on genotypes and phenotypes was used in the step 2 of the two-sample approach, enable detailed SNP harmonization (such as the alignment of genotyping results) to be completed.

There are several weaknesses in this study. This study aims at elucidating the inconclusive results from observation studies in Asian women. The step 2 population selected unrelated female subjects whose principal-components analysis showed at least 86% of Asian ancestry, however, the step 1 IV SNP selection was conducted within all possible populations, causing suspicious population stratification in this study. By virtue of limited GWA studies on age at menarche and age at menopause in Asian populations, all primary GWA studies were used to select IV SNPs, which might limit our ability to select Asian women specific IV SNPs. On the other hand, GWA replication studies found most of the genetic determinants of age at menarche and age at menopause might be shared between European and Asian women, with some reached nominal statistical significance while other showed the same association directions[146, 193, 194]. Another point for future improvement is genomic imputation. In the SNPs selection process, there were 209 menarche SNPs and 95 menopause SNPs identified in step 1 but not genotyped in FLCCA. If these SNPs could be imputed using reference population such as 1000 Genome Project, HapMap Project, or potentially one's own population with those SNPs tested, the number of IV SNPs used in the final MRs may be considerably increased. The published FLCCA GWA paper described that LiftOver was applied to update the genomic coordinates

from Build 36 to Build 38 and IMPUTE2 were applied to conduct genomic imputation[148], although imputed data were not provided in dbGaP database. Without smaller-sized corresponding data in PLINK or other formats, the raw Illumina reads (523 gigabytes of data) provided by dbGaP needs facilities of advanced computing capabilities (including LiftOver and IMPUTE2) to reproduce the imputation done by FLACCA research team. The third drawback of this study is the interpretability of PRS. Due to lack of self-reported or direct measure of ages at menarche or menopause for individual subject in the study population, the calculated PRS lacks biological representation. A potential improvement for this issue is scaling, in which the PRS is divided by the regression coefficient of a linear regression of PRS on age at menarche. This regression coefficient will require an external population with these candidate SNPs genotyped and everyone's age at menarche/menopause reported[168].

CHAPTER 5 Conclusion and public health implication

For Ami 1, for postmenopausal Asian women, later menopause, more lifetime ovulatory cycles, and fewer pregnancies were associated with increased risk of lung cancer. This incremental risk appeared larger among ever smokers than their never-smoking counterparts. The potential etiological clues of estrogen in the occurrence of lung cancer need to be further explored by more epidemiologic studies with biomarkers measurements. The identification of relationships between hormonal factors and the risk of lung cancer could inform preventive strategies and therapeutic regimes. Although causal interaction was not verified, the effect modification by smoking status could potentially add rationale to tobacco smoking cessation interventions and to reduce environmental tobacco smoking among female populations[1].

In Aim 2, the pooled analysis corroborated in Asian populations the positive association between lung cancer and menopause, older age at menarche, and older age at first birth, and the inverse association between lung cancer and livebirth and OC use. This pooled analysis also discovered prominently higher probability of lung cancer diagnosis among Asian women with late onset of menarche. These observations were especially important as they provided quality comparison with and contrast to studies composed of Caucasian and other populations. The findings in this study also contributed to insights into lung cancer etiology in women and could inform advanced preventive strategies[3].

In Aim 3 of this dissertation, the MR utilized two-sample approach and PRS analyses to test and measure the causal effect of age at menarche and age at menopause on lung cancer occurrence in Asian women. Due to limited power, an actual effect could not be excluded based on this study. In this study, we do not have sufficient power to support the causal effects of age at menarche and age at menopause on the risk of lung cancer[4].

Observations indicate that steroid hormones, genetic variants, menstrual/reproductive factors may interplay with each other and may have effects on the risk of lung cancer. Research on these interplays and effects are fundamental for innovative integrated approaches like systems sciences that consider the individual's complexity for the best preventive and therapeutic strategies e.g., targeted therapy/prevention with steroid hormone related biomarkers. This dissertation research is especially meaningful for the targeted prevention and therapy for Asian women in the era of personalized public health and medicine[45, 48, 195].

Tables and Figures

Figure 1-1. Age standardized incidence and mortality rates of lung cancer in two sexes

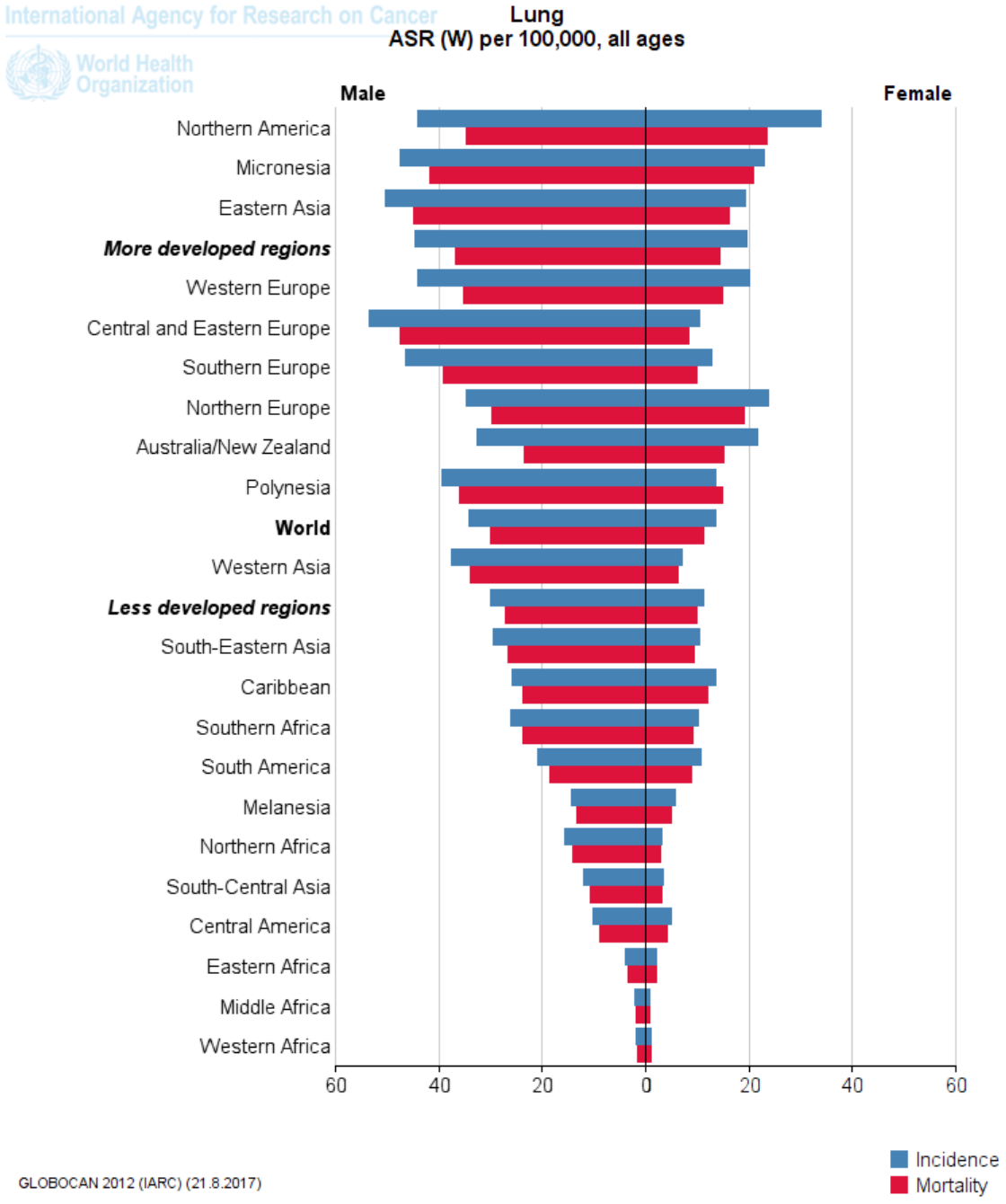


Figure 1-2. Age standardized (World) incidence rates per 100,000 by year in selected populations for lung cancer in men (left panel) and women (right panel), 1975-2012[34]

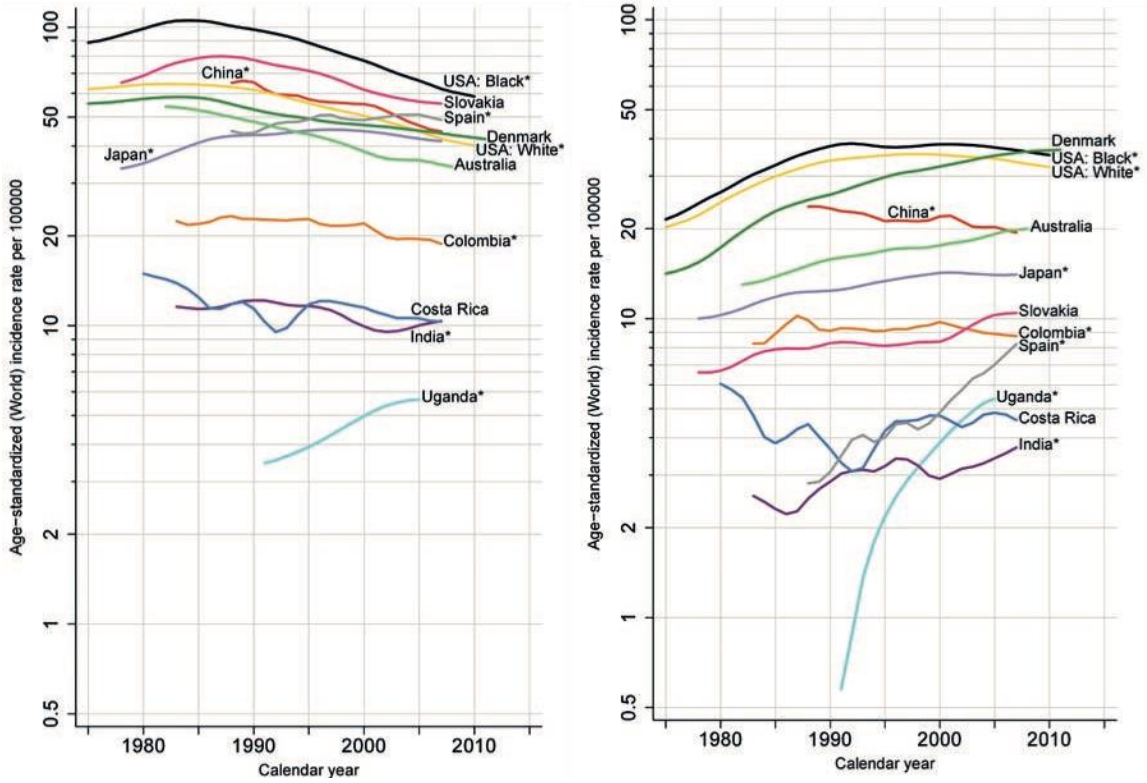


Table 1-1. Frequency distribution of histologic subtypes of lung cancer (USA) [9]

Type	Frequency
Non-small cell lung cancer (NSCLC)	80%
Adenocarcinoma	40%
Squamous cell (epidermoid) carcinoma (SCC)	25-30%
Large cell (undifferentiated) carcinoma	10-15%
Small cell lung cancer (SCLC)	10-15%
Other types	<5%

Table 1-2 Summary of the findings in the literature

	ILCCO Pooled analysis[48, 49]	2012 Meta-analysis[50]	2017 China study[58]	2015 WHI[53]	2015 Singapore cohort[56]	2013 Shanghai Textile workers cohort[55]	2012 Singapore case-control study[54]
Study design	Pooled analysis	Meta-analysis	Case-control	Prospective cohort	Prospective cohort	Prospective cohort	Case-control
Age at menarche	NS	Oldest vs youngest age category in NA: RR=0.83, 95% CI 0.73, 0.94)	NS	Trend of decreased risk with older age, P_{trend}=0.04	NS	NS	NS
Age at menopause	>51 vs <=43 in SCC: OR=3.67, 95% CI=1.15, 11.67	NS	>50 vs <=50 OR=1.47, 95% CI=1.021, 2.119	50+ vs <40: OR=0.73, 95% CI=0.62, 0.85	NS	49-51 vs <=48: HR=1.22, 95% CI=1.03, 1.46	>=52 vs <=48: OR=1.34, 95% CI=1.03, 1.74
Menstrual cycle length	--	Longest vs shortest menstrual cycle: RR=0.72, 95% CI=0.57, 0.90	--	--	--	--	>30 vs <30: OR=0.61, 95%CI=0.42, 0.88
Parity/ gravidity	Parity yes vs no (pre): OR=1.74, 95% CI=1.03, 2.93; More than three vs 0 children (pre): OR=2.87, 95% CI=1.28, 6.44, (post): OR=0.78, 95%CI=0.61, 0.99	NS	NS	Trend of increased risk with increased number of live births, P_{trend}=0.03	Pregnancy yes vs no: HR=0.53, 95% CI=0.38, 0.74; protective trend of gravidity(# preg.): P_{trend}<0.0001; protective trend of parity(# of deliveries): P_{trend}<0.0001	Pregnancy yes vs no: NS; gravidity: NS; >=5 vs 0 live birth: HR=0.70, 95% CI=0.51, 0.95	>=5 vs 0 children: OR=0.61, 95%CI=0.43, 0.88;
Breast feeding	NS	--	NS	--	NS	NS	--
Reproductive window	--	--	--	--	NS	NS	NS
# menstrual cycles	--	--	--	--	--	--	--
OC	OR=0.81, 95% CI=0.68, 0.97	NS	OR=1.84, 95% CI=1.111, 3.06	NS	NS	--	NS
HRT	OR=0.77, 95% CI=0.61, 0.94	NS	--	<5 years E+P use vs nonuser: HR=0.84, 95% CI=0.72, 0.98	NS	--	NS
Other significant association	post vs pre: OR=1.92, 95% CI=1.5, 2.46; Oophorectomy OR=1.45, 95% CI=1.12,1.87					Tubal ligation: HR=0.83 95%CI=0.72, 0.97	Age at first birth 26-33 vs <=20: OR=1.92, 95% CI=1.37, 2.69

NS=null/not significant associated; OC=oral contraceptive use; HRT=hormone replacement therapy; --= no report; NA=North America; E+P=Estrogen plus Progestin; pre=premenopausal; post=post-menopausal

Figure 1-3. Framework of Instrumental Variable analysis/ Mendelian randomization

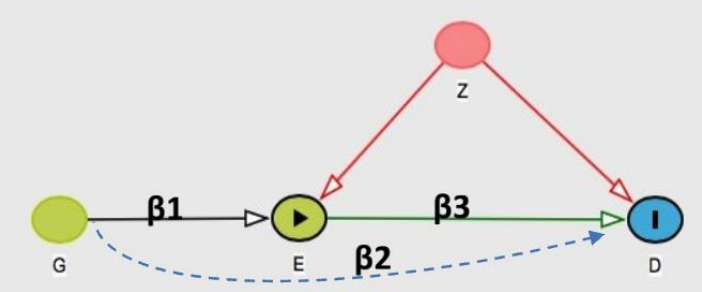


Table 2-1. SNP list to be chosen for Aim 1 G by E study (Aim1)

No.	SNP	Gene	Pathway	MAF
Micro RNA Related				
1	rs1804429	CXCL12	Associated with hematopoiesis/lymphopoiesis	0.093 (G)
2	rs10519613	IL15	Associated with hematopoiesis/lymphopoiesis	0.489 (A)
3	rs12828	WWOX	Associated with apoptotic functions	0.367 (A)
4	rs896849	TP53INP1	Associated with apoptotic functions	0.133 (C)
5	rs3816757	TAB3	Associated with the MAPKinase Signaling Pathway	0.189 (G)
6	rs11614913	miR-196a2	miRNA genes	0.477 (C)
7	rs2910164	pre-miR-146a	miRNA genes	0.444 (C)
8	rs895819	miR-27	miRNA genes	0.314 (C)
9	rs7372209	miR-26a1	miRNA genes	0.326 (T)
10	rs3742330	Dicer1	Genes involved in miRNA processing and maturation	0.267 (G)
11	rs4961280	Ago2	Genes involved in miRNA processing and maturation	0.111 (A)
12	rs14035	Ran	Genes involved in miRNA processing and maturation	0.186 (T)
13	rs197412	Gemin3	Genes involved in miRNA processing and maturation	0.337 (C)
14	rs2740348	Gemin4	Genes involved in miRNA processing and maturation	0.125 (C)
15	rs7813	Gemin4	Genes involved in miRNA processing and maturation	0.286 (C)
16	rs11077	XPO5	Genes involved in miRNA processing and maturation	0.07 (C)
17	rs9266	KRAS	Associated with immune response and signaling	0.267 (T)
18	rs4072391	IL6R	Associated with immune response and signaling	0.105 (T)
19	rs2126852	RCHY1	Associated with apoptotic functions	0.244 (G)
20	rs7760	TP53INP1	Associated with apoptotic functions	0.128 (G)
21	rs42031	CDK6	Associated with cell cycle progression and proliferation	0.050 (T)
22	rs2075993	E2F2	Associated with cell cycle progression and proliferation	0.430 (A)
23	rs3801790	DOCK4	Associated with immune response and signaling	0.291 (G)
24	rs3929	Rbl2	miR-K12-4-5p	0.2
25	rs2292305	THBS1	miR-K1, miR-K3-3p, miR-K6-3p, miR-K11	0.34

26	rs2273368	Wnt2B	miRNA 449 targets Wnt2b and Axin2 as a potential positive regulator of the Wnt pathway.	0.488 (T)
27	rs2953	CTNNB1	miRNA-589targets CTNNB1 or β-catenin which is an up-regulator of Wnt signaling.	0.244 (G)
28	rs3774923	PPARGC1A	One target gene for miRNA-200a is PPAR γ which permits the interaction with multiple transcription factors. miRNA 200a has been previously observed as a potential negative regulator of the Wnt pathway.	0.232(A)
Stem Cell Related				
1	rs6815391	Rex1	Stem cell maintenance	0.38(C)
2	rs13409	Oct4	Stem cell maintenance	0.34 (T)
3	rs3130932	Oct4	Stem cell development	0.43 (G)
4	rs2228224	GLI1	Polycomb	0.27 (A)
5	rs1126497	EpCAM	Epithelial to mesenchymal transition	0.17 (T)
6	rs3740535	Ctbp2	Stem cell maintenance	0.19 (A)
7	rs915894	Notch4	Notch signaling	0.46 (A)
8	rs1046472	HEY1	Notch signaling	0.22 (A)
9	rs3734637	HEY2	Notch signaling	0.16 (C)
10	rs11364	HES2	Notch signaling	0.19 (A)
11	rs520692	Notch4	Notch signaling	0.17 (G)
12	rs9972231	JAG2	Notch signaling	0.15 (T)
13	rs8708	HES2	Notch signaling	0.12 (G)
14	rs1033583	DLL1	Notch signaling	0.31 (C)
15	rs1421	DLL1	Notch signaling inhibitor	0.15 (G)
16	rs2269700	Dec1	Notch signaling	0.23(C)
17	rs2229971	Notch1	Notch signaling	0.18 (T)
18	rs2240308	AXIN2	Wnt signaling	0.38 (A)
19	rs3815188	Notch1	Notch signaling	0.39 (A)
20	rs3729629	WNT2	Wnt ligands bind to frizzled transmembrane receptors to activate the Wnt pathway.	0.293(C)
21	rs4730775	WNT2	Wnt ligands bind to frizzled transmembrane receptors to activate the Wnt pathway.	0.183 (T)
22	rs4835761	WNT8A	Wnt ligands bind to frizzled transmembrane receptors to activate the Wnt pathway.	0.427 (G)
23	rs3750145	FZD1	Frizzled proteins bind to Wnt ligands and are thought to downregulate Wnt signaling when overexpressed.	0.137 (G)
24	rs2241802	FZD3	Frizzled proteins bind to Wnt ligands and are thought to downregulate Wnt signaling when overexpressed.	0.451 (A)
25	rs222851	DVL2	Dishevelled, Axin, and GSK3β are cytoplasmic proteins that interact with β-catenin.	0.402 (G)
26	rs1981492	AXIN1	Dishevelled, Axin, and GSK3β are cytoplasmic proteins that interact with β-catenin.	0.256 (A)
27	rs6754757	TCF7L1	TCF/LEF complex binds to β-catenin to activate transcription of downstream genes.	0.256 (G)
HIF-1α pathway				
1	rs2295778	HIF1AN	HIF	0.23
2	rs2057482			0.24(T)

3	rs2301113			0.42(C)
NF-κB Pathway				
1	rs1050851	NFKBIA	NFκB	0.02
2	rs2230793	IKBKAP	NFκB	0.27
3	rs1538660	IKBKAP	NFκB	0.23
4	rs12894467	miR-300	NFκB	0.20
5	rs8904	NFKBIA	NFκB	0.40
6	rs696	NFKBIA	NFκB	0.40
7	rs3204145	IKBKAP	NFκB	0.23

Table 3-1. Distribution of Demographic and Major Risk Factors in Cases and Controls

	Lung cancer	Controls	*P*-value
Total Number	680(27.33)	1808(72.67)	
	Mean(SD)	**Mean(SD)**	
Age(continuous)	66.79 (9.36)	67.37 (9.32)	0.1641
	N(column%)	**N(column%)**	
Education			0.1783
Illiterate	554(81.71)	1431(79.50)	
Primary School	106(15.63)	294(16.33)	
Middle School +	18(2.65)	75(4.17)	
Income			0.1783
<1000	130(19.88)	416(23.44)	
1000-1499	131(20.03)	382(21.52)	
1500-2499	177(27.06)	459(25.86)	
>=2500	216(33.03)	518(29.18)	
County			**<0.0001**
Dafeng	152(22.35)	597(33.02)	
Ganyu	185(27.21)	337(18.64)	
Chuzhou	120(17.65)	365(20.19)	
Tongshan	223(32.79)	509(28.15)	
Tobacco smoking			**<0.0001**
Never	499(73.38)	1464(80.97)	
Ever	181(26.62)	344(19.03)	
Pack-year			**<0.0001**
0	499 (73.38)	1464(80.97)	
<10	25(3.68)	68(3.76)	
[10,20)	24(3.53)	63(3.48)	
[20,30)	51(7.50)	91(5.03)	
[30,40)	19(2.79)	45(2.49)	
[40,50)	25(3.68)	33(1.83)	
[50,60)	12(1.76)	24(1.33)	
>=60	25(3.68)	20(1.11)	
BMI			**<0.0001**
<18.5	115(17.09)	155(8.61)	
18.5 to <24	388(57.65)	998(55.41)	
24 to <28	137(20.36)	497(27.60)	
>=28	33(4.90)	151(8.38)	
Family history of lung cancer			**0.0117**
No	655(96.32)	1773(98.06)	
Yes	25(3.68)	35(1.94)	

Table 3-2. Menstrual and reproductive factors in association with the risk of lung cancer in the entire study population

	All					
	Cases, n=680		Ctrls, n=1808		Adjusted OR[1]	SB-adjusted[1] OR[1]
	N	%	N	%	(95% CI)	(95% CI)
Menstrual Characteristics						
Age at menarche						
<=15	224	33.33	639	35.56	1.00(Ref)	1.00(Ref)
16-17	262	38.99	689	38.34	1.20(0.96 , 1.51)	1.20(0.96 , 1.50)
>=18	186	27.68	469	26.10	1.29(1.00-, 1.68)	1.29(1.00-, 1.66)
P_{trend}[4]					**0.046**	**0.043**
As a continuous variable[8]					1.05(1.00-, 1.10)	1.05(1.00-, 1.10)
Age at menopause[5]						
<46	62	9.84	189	11.09	1.00(Ref)	1.00(Ref)
46-54	451	71.59	1307	76.66	1.02(0.73 , 1.43)	1.01(0.73 , 1.38)
>54	117	18.57	209	12.26	**1.65(1.10 , 2.48)**	**1.61(1.10 , 2.36)**
P_{trend}					**0.004**	**0.004**
As a continuous variable[8]					**1.03(1.01 , 1.06)**	**1.03(1.01 , 1.06)**
Reproductive window						
<=32	227	35.80	651	38.11	1.00(Ref)	1.00(Ref)
33-35	181	28.55	511	29.92	0.98(0.76 , 1.25)	0.98(0.77 , 1.24)
>=36	226	35.65	546	31.97	1.10(0.87 , 1.40)	1.10(0.87 , 1.40)
P_{trend}					0.441	0.406
As a continuous variable[8]					1.01(0.99 , 1.03)	1.01(0.99 , 1.03)
Reproductive History						
Parity[6]						
0 or 1	116	17.08	217	12.00	1.00(Ref)	1.00(Ref)
2-3	305	44.92	864	47.79	**0.68(0.51 , 0.91)**	**0.70(0.53 , 0.93)**
4 or more	258	38	727	40.21	**0.72(0.53 , 0.97)**	**0.74(0.55 , 0.99)**
P_{trend}					0.177	0.18
As a continuous variable[8]					0.95(0.89 , 1.01)	0.95(0.89 , 1.01)
Gravidity[6]						
0 or 1	104	15.32	195	10.79	1.00(Ref)	1.00(Ref)
2-3	275	40.50	773	42.75	**0.69(0.50 , 0.93)**	**0.71(0.53 , 0.95)**
4 or more	300	44.18	840	46.46	0.78(0.58 , 1.06)	0.80(0.60 , 1.08)
P_{trend}					0.583	0.587
As continuous variable[8]					0.96(0.91 , 1.02)	0.96(0.91 , 1.02)
Number of live birth[6]						
0 or 1	118	17.38	226	12.50	1.00(Ref)	1.00(Ref)
2-3	313	46.10	887	49.06	**0.69(0.52 , 0.92)**	**0.71(0.54 , 0.94)**
4 or more	248	36.52	695	38.44	**0.73(0.54 , 0.99)**	0.75(0.56 , 1.01)
P_{trend}					0.227	0.227
As a continuous variable[8]					0.95(0.89 , 1.01)	0.95(0.89 , 1.01)
Life time abortion						
Never	631	92.93	1650	91.26	1.00(Ref)	1.00(Ref)
Ever	48	7.07	158	8.74	1.03(0.70 , 1.51)	1.01(0.70 , 1.45)
As a continuous variable[8]					1.08(0.84 , 1.39)	1.05(0.83 , 1.34)
Outcome of first pregnancy[7]						
Live birth	631	94.89	1656	94.04	1.00(Ref)	1.00(Ref)
Stillbirth	19	2.86	51	2.90	0.88(0.48 , 1.61)	0.91(0.52 , 1.58)
	14	2.11	46	2.61	1.02(0.53 , 1.97)	1.03(0.57 , 1.87)
Ectopic	1	0.15	1	0.06	NA	0.91(0.24 , 3.49)
Induced	0	0	6	0.34	NA	NA
Number of Ovulatory Cycles						
<=368	182	30.18	536	33.58	1.00(Ref)	1.00(Ref)
(368, 415]	192	31.84	537	33.65	0.96(0.74 , 1.24)	0.96(0.75 , 1.23)
>415	229	37.98	523	32.77	1.21(0.94 , 1.55)	1.21(0.95 , 1.55)

P_{trend}					0.123	0.113
As a continuous variable(per 13 ovulatory					**1.02(1.00+, 1.04)**	**1.02(1.00+, 1.04)**
Exogenous Hormone						
Oral Contraceptive use						
Never	635	96.5	1649	94.66	1.00(Ref)	1.00(Ref)
Ever	23	3.50	93	5.34	0.93(0.56 , 1.55)	0.93(0.58 , 1.50)

Notation:

1. Odds ratios and 95% confidence intervals adjusted for age (as a continuous variable), smoking status (ever or never), pack-years of smoking, family history of lung cancer (yes or no), income, education, county of residence, and BMI.
2. Odds ratios and 95% confidence intervals adjusted for age (as a continuous variable), family history of lung cancer (yes or no), income, education, county of residence, and BMI.
3. Odds ratios and 95% confidence intervals adjusted for age (as a continuous variable), pack-years of smoking, family history of lung cancer (yes or no), income, education, county of residence, and BMI.
4. Mantel trend test.
5. Additional adjustment for age at menarche (as a continuous variable).
6. Additional adjustment for length of reproductive window.
7. Additional adjustment for age at first birth
8. Absolute number/count as the continuous variable

Table 3-3. Menstrual and reproductive factors in association with the risk of lung cancer, by smoking status

	Never Smokers						Ever Smokers					
	Cases, n=499		Ctrls, n=1464		Adjusted OR[2]	SB-adjusted OR[2]	Cases, n=181		Ctrls, n=344		Adjusted OR[3]	SB-adjusted OR[3]
	N	%	N	%	(95% CI)	(95% CI)	N	%	N	%	(95% CI)	(95% CI)
Menstrual Characteristics												
Age at menarche												
<=15	175	35.57	553	37.93	1.00(Ref)	1.00(Ref)	49	27.22	86	25.37	1.00(Ref)	1.00(Ref)
16-17	187	38.01	534	36.63	1.25(0.96 , 1.64)	1.26(0.98 , 1.63)	75	41.67	155	45.72	0.94(0.57 , 1.53)	0.94(0.60 , 1.48)
>=18	130	26.42	371	25.45	1.34(0.99 , 1.82)	**1.35(1.01 , 1.80)**	56	31.11	98	28.91	1.01(0.59 , 1.74)	1.02(0.62 , 1.67)
P_{trend}[4]					**0.050**	**0.03**					0.962	0.953
As a continuous variable[8]					1.04(0.98 , 1.11)	1.05(0.99 , 1.11)					1.05(0.94 , 1.17)	1.05(0.94 , 1.17)
Age at menopause[5]												
<46	48	10.39	147	10.71	1.00(Ref)	1.00(Ref)	14	8.33	42	12.65	1.00(Ref)	1.00(Ref)
46-54	319	69.05	1041	75.82	0.90(0.61 , 1.33)	0.91(0.64 , 1.30)	132	78.57	266	80.12	1.48(0.72 , 3.06)	1.23(0.68 , 2.21)
>54	95	20.56	185	13.47	1.45(0.91 , 2.29)	1.45(0.95 , 2.20)	22	13.1	24	7.23	2.48(0.94 , 6.51)	1.80(0.85 , 3.84)
P_{trend}					**0.035**	**0.023**					0.066	0.077
As a continuous variable[8]					1.03(1.00-, 1.06)	**1.03(1.00+, 1.06)**					1.04(0.98 , 1.10)	1.04(0.98 , 1.10)
Reproductive window												
<=32	151	32.54	503	36.53	1.00(Ref)	1.00(Ref)	76	44.71	148	44.71	1.00(Ref)	1.00(Ref)
33-35	134	28.88	409	29.70	1.00(0.75 , 1.35)	1.03(0.78 , 1.37)	47	27.65	102	30.82	0.79(0.48 , 1.30)	0.82(0.51 , 1.31)
>=36	179	38.58	465	33.77	1.13(0.86 , 1.50)	1.16(0.89 , 1.51)	47	27.65	81	24.47	0.95(0.57 , 1.59)	0.97(0.60 , 1.57)
P_{trend}					0.375	0.274					0.749	0.778
As a continuous variable[8]					1.01(0.98 , 1.04)	1.01(0.99 , 1.04)					1.01(0.96 , 1.06)	1.01(0.96 , 1.06)
Reproductive History												
Parity[6]												
0 or 1	80	16.06	176	12.02	1.00(Ref)	1.00(Ref)	36	19.89	41	11.92	1.00(Ref)	1.00(Ref)
2-3	242	48.59	753	51.43	**0.69(0.49 , 0.97)**	0.73(0.53 , 1.00+)	63	34.81	111	32.27	0.67(0.35 , 1.27)	0.76(0.43 , 1.35)
4 or more	176	35.34	535	36.54	0.74(0.52 , 1.08)	0.84(0.60 , 1.18)	82	45.30	192	55.81	**0.52(0.28 , 0.97)**	0.60(0.35 , 1.03)
P_{trend}					0.332	0.62					0.114	0.116
As a continuous variable[8]					0.95(0.88 , 1.03)	0.97(0.90 , 1.04)					0.91(0.81 , 1.01)	0.91(0.81 , 1.01)
Gravidity[6]												
0 or 1	71	14.26	159	10.86	1.00(Ref)	1.00(Ref)	33	18.23	36	10.47	1.00(Ref)	1.00(Ref)
2-3	222	44.58	677	46.24	0.73(0.51 , 1.05)	0.77(0.55 , 1.07)	53	29.28	96	27.91	0.57(0.29 , 1.12)	0.67(0.37 , 1.21)
4 or more	205	41.16	628	42.90	0.82(0.57 , 1.20)	0.92(0.65 , 1.30)	95	52.49	212	61.63	0.54(0.29 , 1.00+)	0.62(0.36 , 1.08)
P_{trend}					0.684	0.902					0.268	0.263
As continuous variable[8]					0.98(0.91 , 1.05)	1.00(0.93 , 1.07)					**0.89(0.81 , 0.99)**	**0.89(0.81 , 0.99)**
Number of live birth[6]												
0 or 1	82	16.47	183	12.50	1.00(Ref)	1.00(Ref)	36	19.89	43	12.5	1.00(Ref)	1.00(Ref)
2-3	249	50	770	52.60	**0.69(0.49 , 0.98)**	0.74(0.54 , 1.01)	64	35.36	117	34.01	0.67(0.36 , 1.27)	0.76(0.43 , 1.33)
4 or more	167	33.53	511	34.90	0.75(0.52 , 1.09)	0.84(0.60 , 1.18)	81	44.75	184	53.49	0.56(0.31 , 1.04)	0.64(0.37 , 1.09)

P_{trend}					0.339	0.58					0.206	0.205
As a continuous variable[8]					0.94(0.87 , 1.02)	0.94(0.87 , 1.02)					0.92(0.82 , 1.03)	0.92(0.82 , 1.03)
Life time abortion												
Never	463	92.97	1351	92.28	1.00(Ref)	1.00(Ref)	168	92.82	299	86.92	1.00(Ref)	1.00(Ref)
Ever	35	7.03	113	7.72	1.29(0.81 , 2.06)	1.23(0.81 , 1.87)	13	7.18	45	13.08	0.62(0.31 , 1.25)	0.66(0.36 , 1.22)
As a continuous variable[8]					0.66(0.38 , 1.16)	1.20(0.92 , 1.56)					0.66(0.38 , 1.16)	0.68(0.41 , 1.13)
Outcome of first pregnancy[7]												
Live birth	460	94.65	1361	94.91	1.00(Ref)	1.00(Ref)	171	95.53	295	90.21	1.00(Ref)	1.00(Ref)
Stillbirth	15	3.09	36	2.51	1.05(0.51 , 2.15)	1.15(0.62 , 2.12)	4	2.23	15	4.59	0.43(0.11 , 1.61)	0.64(0.26 , 1.60)
Miscarriage	11	2.26	1	0.07	1.68(0.76 , 3.69)	1.59(0.81 , 3.11)	3	1.68	17	5.20	0.27(0.07 , 1.01)	0.49(0.20 , 1.19)
Ectopic Preg	0	0	29	2.02	NA	NA	1	0.56	0	0	NA	NA
Induced	0	0	6	0.42	NA	NA	0	0	0	0	NA	NA
Number of Ovulatory Cycles												
<=366	124	27.93	413	31.97	1.00(Ref)	1.00(Ref)	58	36.48	123	40.46	1.00(Ref)	1.00(Ref)
367-413	139	31.31	432	33.44	0.99(0.73 , 1.34)	0.97(0.73 , 1.30)	53	33.33	105	34.54	0.91(0.55 , 1.52)	0.92(0.57 , 1.47)
>=414	181	40.77	447	34.60	1.18(0.88 , 1.59)	1.22(0.92 , 1.61)	48	30.19	76	25	1.16(0.68 , 2.00)	1.15(0.70 , 1.89)
P_{trend}					0.233	0.135					0.63	0.632
As a continuous variable(per 13 ovulatory cycles)[8]					1.02(0.99 , 1.04)	1.02(1.00-, 1.04)					1.02(0.98 , 1.06)	1.02(0.98 , 1.07)
Exogenous Hormone												
Oral Contraceptive use												
Never	465	96.47	1327	95.06	1.00(Ref)	1.00(Ref)	170	96.59	312	93.13	1.00(Ref)	1.00(Ref)
Ever	17	3.53	69	4.94	1.16(0.63 , 2.14)	1.11(0.64 , 1.93)	6	3.41	23	6.87	0.58(0.22 , 1.54)	0.69(0.32 , 1.49)

Notation:

1. Odds ratios and 95% confidence intervals adjusted for age (as a continuous variable), smoking status (ever or never), pack-years of smoking, family history of lung cancer (yes or no), income, education, county of residence, and BMI.
2. Odds ratios and 95% confidence intervals adjusted for age (as a continuous variable), family history of lung cancer (yes or no), income, education, county of residence, and BMI.
3. Odds ratios and 95% confidence intervals adjusted for age (as a continuous variable), pack-years of smoking, family history of lung cancer (yes or no), income, education, county of residence, and BMI.
4. Mantel trend test.
5. Additional adjustment for age at menarche (as a continuous variable).
6. Additional adjustment for length of reproductive window.
7. Additional adjustment for age at first birth
8. Absolute number/count as the continuous variable

Table 3-4. Interaction with smoking status

Factor		Case/Ctrl	aOR(95%CI)[1]	Interactions (95%CI)[1]
Menarche at 17 or later	Ever smoking			
No	No	275/838	1.00(Ref)	
No	Yes	94/170	**2.36 (1.70, 3.27)**	RERI= -0.43 (-1.36, 0.5)
Yes	No	217/620	**1.28 (1.02, 1.61)**	ROR= 0.73 (0.47, 1.14)
Yes	Yes	86/169	**2.21 (1.56, 3.12)**	
Menopause at 55 or later	Ever smoking			
No	No	367/1188		
No	Yes	146/308	**1.98 (1.51, 2.59)**	RERI= 0.87 (-1.39, 3.12)
Yes	No	95/185	**1.60 (1.19, 2.15)**	ROR= 1.09 (0.53, 2.25)
Yes	Yes	22/24	**3.45 (1.80, 6.60)**	
Parity=0, 1 or 2	Ever smoking			
No	No	335/1069		
No	Yes	129/276	**1.86 (1.40, 2.48)**	RERI= 0.96 (-0.39, 2.3)
Yes	No	163/395	**1.32 (1.03, 1.69)**	ROR= 1.28 (0.76, 2.15)
Yes	Yes	52/68	**3.13 (2.03, 4.83)**	
Gravidity=0,1 or 2	Ever smoking			
No	No	352/1111		
No	Yes	132/290	**1.77 (1.33, 2.34)**	**RERI= 1.71 (0.03, 3.38)**
Yes	No	146/353	1.26 (0.98, 1.62)	ROR= 1.68 (0.98, 2.89)
Yes	Yes	49/54	**3.73 (2.36, 5.90)**	
#live birth=0, 1 or 2	Ever smoking			
No	No	333/1058		
No	Yes	128/273	**1.85 (1.39, 2.47)**	RERI= 0.95 (-0.36, 2.27)
Yes	No	165/406	**1.30 (1.01, 1.66)**	ROR= 1.29 (0.77, 2.16)
Yes	Yes	53/71	**3.10 (2.02, 4.76)**	

Notation:

Point estimates and 95% confidence intervals were adjusted for age (as a continuous variable), smoking status (ever or never), family history of lung cancer (yes or no), income, education, county of residence, and BMI (categorical).

Table 3-5. The Distribution of Demographic and Major Risk Factors in Cases and Controls in the genotyped population in Aim 1

	Lung cancer	Controls	*P*-value
Total Number	191(25.30)	564(74.70)	
	Mean(SD)	**Mean(SD)**	
Age (continuous)	65.69(8.72)	67.34(8.53)	**0.0219**
	N(Column%)	**N(Column%)**	
Education			0.4769
Illiterate	164(85.86)	465(82.45)	
Primary School	22(11.52)	85(15.07)	
Middle School	5(2.62)	14(2.48)	
Income			0.7509
<1000	35(18.82)	92(16.46)	
1000-1499	36(19.35)	122(21.82)	
1500-2499	59(31.72)	166(29.7)	
≥2500	56(30.11)	179(32.02)	
County			**<0.001**
Dafeng	130(68.06)	504(89.36)	
Ganyu	61(31.94)	60(10.64)	
Tobacco smoking			0.183
Never	113(59.16)	364(64.54)	
Ever	78(40.84)	200(35.46)	
Pack-year			**0.0285**
0	113(59.16)	364(64.54)	
<10	11(5.76)	40(7.09)	
[10, 20)	9(4.71)	40(7.09)	
[20, 30)	14(7.33)	47(8.33)	
[30,40)	11(5.76)	25(4.43)	
[40, 50)	14(7.33)	16(2.84)	
[50,60)	7(3.66)	17(3.01)	
≥60	12(6.28)	15(2.66)	
BMI			**<0.001**
<18.5	56(29.32)	66(11.72)	
[18.5, 24)	97(50.79)	322(57.19)	
[24, 28)	27(14.14)	141(25.04)	
≥28	11(5.76)	34(6.04)	
Family history of lung cancer			0.7725
No	183(95.81)	543(96.28)	
Yes	8(4.19)	21(3.72)	

Table 3-6. Comparison between genotyped controls and controls not genotyped

	Genotyped ctrls	Ctrls not genotyped	*P*-value
Total Number	564(74.70)	1244(71.78)	
	Mean(SD)	**Mean(SD)**	
Age (continuous)	67.34(8.53)	67.39(9.65)	0.9227
	N(Column%)	**N(column%)**	
Education			**0.0261**
Illiterate	465(82.45)	966(78.16)	
Primary School	85(15.07)	209(16.91)	
Middle School +	14(2.48)	61(4.94)	
Income			**0.0000**
<1000	92(16.46)	324(26.64)	
1000-1499	122(21.82)	260(21.38)	
1500-2499	166(29.7)	293(24.1)	
≥2500	179(32.02)	339(27.88)	
County			**0.0000**
Dafeng	504(89.36)	93(7.48)	
Ganyu	60(10.64)	277(22.27)	
Chuzhou	0(0.00)	365(29.34)	
Tongshan	0(0.00)	509(40.92)	
Tobacco smoking			**0.0000**
Never	364(64.54)	1100(88.42)	
Ever	200(35.46)	144(11.58)	
Pack-year			**0.0000**
0	364(64.54)	1100(88.42)	
<10	40(7.09)	28(2.25)	
[10, 20)	40(7.09)	23(1.85)	
[20, 30)	47(8.33)	44(3.54)	
[30,40)	25(4.43)	20(1.61)	
[40, 50)	16(2.84)	17(1.37)	
[50,60)	17(3.01)	7(0.56)	
≥60	15(2.66)	5(0.4)	
BMI			**0.0007**
<18.5	66(11.72)	89(7.19)	
[18.5, 24)	322(57.19)	676(54.6)	
[24, 28)	141(25.04)	356(28.76)	
≥28	34(6.04)	117(9.45)	
Family history of lung cancer			**0.0002**
No	543(96.28)	1230(98.87)	
Yes	21(3.72)	14(1.13)	

Figure 3-1. SNP selection flowchart

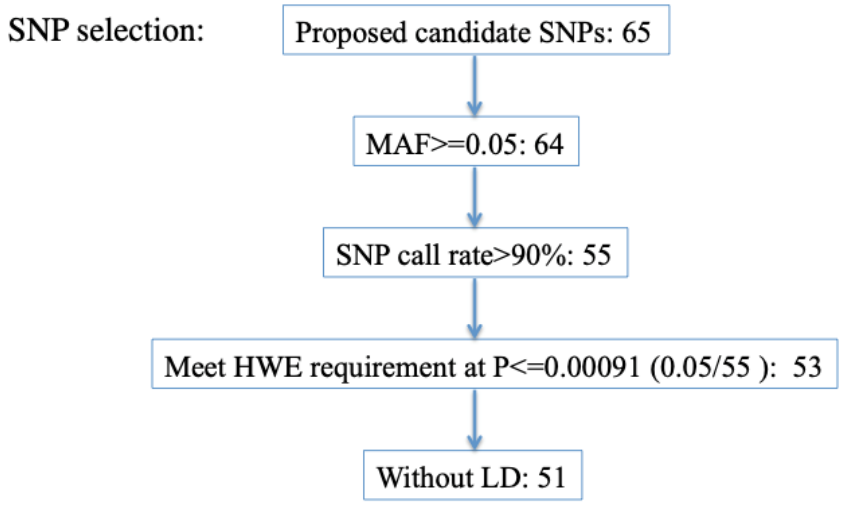


Table 3-7. Candidate SNPs and risk of lung cancer in post-menopausal women in Jiangsu Study

	All				
dbSNP no.	ca/co	cOR	aOR	sbOR	miOR
Total	191/564				
Micro RNA Related					
rs1804429					
T:T	164/459	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
G:T	23/72	0.89(0.54,1.48)	0.89(0.51,1.56)	0.91(0.54,1.52)	0.88(0.63,1.23)
G:G	0/2	0.00(0.00,I)	0.00(0.00,I)	0.78(0.24,2.53)	NA
Log-Add		0.85(0.52,1.39)	0.83(0.48,1.43)	0.87(0.53,1.45)	0.87(0.61,1.25)
Dominant		0.87(0.53,1.44)	0.85(0.49,1.47)	0.89(0.53,1.49)	0.92(0.49,1.73)
Recessive		0.00(0.00,I)	0.00(0.00,I)	0.85(0.23,3.16)	NA
rs10519613					
C:C	66/190	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:A	88/241	1.05(0.72,1.52)	0.90(0.60,1.36)	0.91(0.62,1.36)	1.03(0.77,1.38)
A:A	29/97	0.86(0.52,1.42)	0.66(0.38,1.16)	0.82(0.63,1.08)	0.96(0.63,1.44)
Log-Add		0.95(0.75,1.20)	0.86(0.66,1.12)	0.84(0.64,1.09)	0.99(0.81,1.21)
Dominant		1.00(0.70,1.41)	0.87(0.59,1.28)	0.84(0.58,1.23)	0.95(0.78,1.15)
Recessive		0.84(0.53,1.32)	0.75(0.46,1.23)	0.73(0.46,1.18)	0.90(0.62,1.31)
rs12828					
G:G	79/208	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	74/240	0.81(0.56,1.17)	0.70(0.46,1.06)	0.72(0.49,1.08)	0.86(0.65,1.14)
A:A	28/77	0.96(0.58,1.59)	0.92(0.53,1.61)	0.97(0.74,1.27)	0.87(0.64,1.20)
Log-Add		0.94(0.73,1.19)	0.89(0.68,1.17)	0.90(0.69,1.17)	0.92(0.79,1.07)

Dominant		0.85(0.60,1.19)	0.75(0.52,1.10)	0.77(0.53,1.12)	0.90(0.67,1.21)
Recessive		1.06(0.67,1.70)	1.11(0.66,1.85)	1.09(0.67,1.78)	1.00(0.73,1.39)
rs896849					
T:T	147/402	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
T:C	32/117	0.75(0.48,1.15)	0.74(0.46,1.20)	0.76(0.49,1.20)	0.89(0.58,1.37)
C:C	7/14	1.37(0.54,3.45)	1.33(0.47,3.80)	1.13(0.69,1.85)	1.29(0.41,4.02)
Log-Add		0.91(0.64,1.27)	0.88(0.61,1.27)	0.90(0.63,1.29)	0.93(0.63,1.38)
Dominant		0.81(0.54,1.22)	0.79(0.51,1.23)	0.82(0.54,1.25)	0.89(0.67,1.17)
Recessive		1.45(0.58,3.65)	1.36(0.48,3.84)	1.24(0.53,2.87)	1.92(0.69,5.33)
rs11614913					
T:T	55/159	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	82/253	0.94(0.63,1.39)	0.92(0.59,1.43)	0.92(0.60,1.40)	0.91(0.70,1.18)
C:C	44/112	1.14(0.71,1.81)	1.23(0.74,2.05)	1.11(0.86,1.42)	1.10(0.76,1.59)
Log-Add		1.06(0.84,1.34)	1.05(0.81,1.35)	1.09(0.85,1.41)	1.06(0.87,1.28)
Dominant		1.00(0.69,1.44)	0.97(0.65,1.46)	1.01(0.68,1.50)	0.98(0.77,1.25)
Recessive		1.18(0.79,1.76)	1.19(0.77,1.84)	1.27(0.83,1.93)	1.04(0.77,1.41)
rs2910164					
C:C	64/206	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
G:C	80/236	1.09(0.75,1.59)	1.15(0.75,1.75)	1.13(0.76,1.69)	1.09(0.75,1.59)
G:G	40/91	1.41(0.89,2.25)	**1.70(1.02,2.85)**	**1.29(1.01,1.66)**	1.14(0.69,1.89)
Log-Add		1.18(0.93,1.48)	**1.30(1.01,1.67)**	1.28(0.99,1.64)	1.06(0.84,1.36)
Dominant		1.18(0.83,1.68)	1.32(0.90,1.93)	1.28(0.88,1.86)	1.03(0.80,1.32)
Recessive		1.35(0.89,2.05)	**1.59(1.01,2.51)**	1.52(0.98,2.35)	1.13(0.80,1.58)
rs895819					
T:T	100/287	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
T:C	71/203	1.00(0.71,1.43)	1.07(0.72,1.58)	1.07(0.73,1.55)	0.90(0.71,1.15)
C:C	15/47	0.92(0.49,1.71)	0.97(0.49,1.93)	0.98(0.70,1.37)	1.02(0.68,1.52)
Log-Add		0.98(0.75,1.26)	1.00(0.76,1.33)	1.02(0.77,1.34)	0.96(0.80,1.16)
Dominant		0.99(0.71,1.38)	1.02(0.71,1.47)	1.05(0.73,1.50)	0.96(0.78,1.19)
Recessive		0.91(0.50,1.68)	0.94(0.48,1.81)	0.95(0.52,1.73)	0.90(0.59,1.37)
rs7372209					
C:C	94/276	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	71/224	0.93(0.65,1.33)	0.92(0.62,1.36)	0.93(0.64,1.35)	0.96(0.76,1.20)
T:T	19/35	1.59(0.87,2.92)	1.74(0.87,3.46)	1.30(0.93,1.81)	1.10(0.65,1.88)
Log-Add		1.11(0.86,1.45)	1.17(0.87,1.56)	1.12(0.84,1.50)	1.00(0.82,1.23)
Dominant		1.02(0.73,1.43)	1.05(0.73,1.51)	1.02(0.72,1.46)	0.99(0.76,1.29)
Recessive		1.65(0.92,2.96)	**1.98(1.03,3.80)**	1.61(0.88,2.95)	1.24(0.73,2.12)
rs3742330					
A:A	74/235	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	82/224	1.16(0.81,1.67)	1.02(0.68,1.52)	1.02(0.69,1.50)	1.03(0.82,1.28)
G:G	30/80	1.19(0.73,1.95)	1.20(0.69,2.09)	1.09(0.83,1.43)	0.97(0.58,1.62)
Log-Add		1.11(0.88,1.40)	1.09(0.84,1.41)	1.07(0.83,1.39)	1.00(0.81,1.23)
Dominant		1.17(0.83,1.64)	1.11(0.76,1.60)	1.06(0.74,1.52)	1.00(0.78,1.30)
Recessive		1.10(0.70,1.74)	1.13(0.68,1.89)	1.16(0.71,1.87)	0.99(0.68,1.44)
rs4961280					

C:C	157/412	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:A	29/98	0.78(0.49,1.22)	0.75(0.46,1.24)	0.78(0.49,1.25)	0.90(0.70,1.16)
A:A	1/10	0.26(0.03,2.07)	0.21(0.02,1.73)	0.59(0.28,1.25)	0.39(0.03,4.44)
Log-Add		0.72(0.48,1.08)	0.69(0.45,1.07)	0.70(0.46,1.06)	0.88(0.68,1.14)
Dominant		0.73(0.47,1.14)	0.70(0.44,1.14)	0.72(0.46,1.14)	0.91(0.67,1.23)
Recessive		0.27(0.03,2.16)	0.26(0.03,2.09)	0.57(0.20,1.61)	0.30(0.04,2.46)
rs14035					
C:C	140/355	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	42/127	0.84(0.56,1.25)	0.94(0.60,1.47)	0.94(0.61,1.44)	0.94(0.65,1.34)
T:T	5/26	0.49(0.18,1.30)	0.69(0.24,2.00)	0.85(0.52,1.39)	0.95(0.43,2.10)
Log-Add		0.78(0.57,1.07)	0.90(0.63,1.28)	0.90(0.63,1.26)	0.95(0.68,1.31)
Dominant		0.78(0.53,1.14)	0.92(0.60,1.40)	0.91(0.60,1.36)	0.86(0.65,1.14)
Recessive		0.51(0.19,1.35)	0.68(0.24,1.94)	0.80(0.35,1.82)	0.84(0.36,1.94)
rs197412					
T:T	93/237	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
T:C	66/238	0.71(0.49,1.02)	0.79(0.53,1.17)	0.80(0.54,1.17)	0.94(0.67,1.31)
C:C	26/56	1.18(0.70,2.00)	1.23(0.69,2.19)	1.10(0.83,1.46)	0.97(0.62,1.50)
Log-Add		0.95(0.74,1.22)	0.97(0.75,1.27)	1.00(0.76,1.30)	0.98(0.78,1.22)
Dominant		0.80(0.57,1.11)	0.85(0.59,1.23)	0.88(0.61,1.25)	0.96(0.80,1.15)
Recessive		1.39(0.84,2.28)	1.29(0.75,2.23)	1.30(0.78,2.18)	1.01(0.63,1.63)
rs2740348					
G:G	144/412	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
G:C	32/91	1.01(0.64,1.57)	1.11(0.68,1.81)	1.10(0.69,1.74)	0.93(0.66,1.33)
C:C	4/13	0.88(0.28,2.74)	0.99(0.29,3.40)	1.00(0.57,1.76)	1.15(0.47,2.82)
Log-Add		0.98(0.68,1.41)	1.05(0.71,1.56)	1.06(0.72,1.55)	0.98(0.77,1.25)
Dominant		0.99(0.65,1.51)	1.08(0.68,1.72)	1.09(0.70,1.69)	0.94(0.71,1.25)
Recessive		0.88(0.28,2.73)	0.93(0.27,3.18)	0.99(0.39,2.48)	0.95(0.30,2.98)
rs7813					
T:T	89/266	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	71/189	1.12(0.78,1.61)	1.27(0.85,1.90)	1.24(0.84,1.83)	0.97(0.71,1.32)
C:C	18/58	0.93(0.52,1.66)	1.03(0.55,1.95)	1.01(0.74,1.38)	0.91(0.54,1.53)
Log-Add		1.01(0.79,1.30)	1.08(0.82,1.41)	1.09(0.83,1.43)	0.96(0.74,1.25)
Dominant		1.08(0.77,1.51)	1.19(0.82,1.73)	1.19(0.83,1.72)	1.00(0.82,1.22)
Recessive		0.88(0.50,1.54)	0.91(0.49,1.66)	0.94(0.54,1.64)	0.89(0.57,1.40)
rs11077					
A:A	165/466	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:C	22/64	0.97(0.58,1.63)	0.81(0.45,1.45)	0.83(0.49,1.43)	0.91(0.68,1.22)
C:C	1/5	0.57(0.07,4.87)	0.39(0.04,4.31)	0.76(0.32,1.79)	0.54(0.06,5.03)
Log-Add		0.92(0.58,1.47)	0.77(0.46,1.30)	0.79(0.49,1.29)	0.90(0.68,1.19)
Dominant		0.94(0.57,1.56)	0.77(0.44,1.35)	0.80(0.47,1.35)	0.88(0.63,1.24)
Recessive		0.57(0.07,4.89)	0.49(0.04,5.64)	0.77(0.24,2.44)	0.66(0.07,6.29)
rs9266					
C:C	124/356	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	56/154	1.04(0.72,1.51)	0.82(0.54,1.24)	0.83(0.56,1.24)	0.91(0.72,1.15)
T:T	10/26	1.10(0.52,2.36)	0.93(0.39,2.19)	0.97(0.64,1.45)	1.03(0.60,1.75)

Log-Add		1.05(0.79,1.39)	0.90(0.66,1.24)	0.89(0.65,1.22)	0.96(0.79,1.16)
Dominant		1.05(0.74,1.49)	0.85(0.57,1.24)	0.84(0.58,1.23)	0.87(0.68,1.12)
Recessive		1.09(0.52,2.30)	1.09(0.47,2.51)	0.99(0.48,2.03)	1.19(0.60,2.34)
rs4072391					
C:C	156/439	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	27/92	0.83(0.52,1.32)	1.09(0.66,1.83)	1.08(0.67,1.74)	0.96(0.64,1.43)
T:T	3/6	1.41(0.35,5.69)	2.20(0.49,9.84)	1.35(0.69,2.65)	2.68(0.59,12.09
Log-Add		0.91(0.61,1.36)	1.14(0.74,1.76)	1.17(0.77,1.79)	1.00(0.69,1.46)
Dominant		0.86(0.55,1.35)	1.09(0.67,1.77)	1.14(0.71,1.81)	1.01(0.74,1.40)
Recessive		1.45(0.36,5.86)	2.12(0.49,9.17)	1.41(0.49,4.03)	2.62(0.63,10.92
rs42031					
A:A	180/484	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:T	9/53	**0.46(0.22,0.94)**	0.55(0.25,1.23)	0.64(0.32,1.26)	0.92(0.55,1.55)
T:T	0/4	0.00(0.00,I)	0.00(0.00,I)	0.54(0.20,1.45)	0.69(0.07,6.48)
Log-Add		**0.43(0.21,0.86)**	**0.43(0.20,0.90)**	0.54(0.29,1.02)	0.92(0.55,1.53)
Dominant		**0.42(0.21,0.88)**	**0.43(0.20,0.93)**	0.56(0.29,1.10)	0.98(0.62,1.55)
Recessive		0.00(0.00,I)	0.00(0.00,I)	0.60(0.18,1.99)	0.84(0.09,8.01)
rs2075993					
G:G	75/192	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
G:A	76/237	0.82(0.57,1.19)	0.82(0.55,1.25)	0.84(0.57,1.25)	0.86(0.65,1.16)
A:A	28/84	0.85(0.52,1.41)	0.75(0.43,1.32)	0.87(0.66,1.15)	0.92(0.65,1.32)
Log-Add		0.90(0.71,1.15)	0.89(0.68,1.16)	0.86(0.66,1.12)	0.95(0.79,1.14)
Dominant		0.83(0.59,1.17)	0.85(0.58,1.24)	0.82(0.56,1.18)	0.91(0.72,1.14)
Recessive		0.95(0.59,1.51)	0.87(0.52,1.45)	0.85(0.52,1.38)	1.05(0.72,1.53)
rs3801790					
A:A	76/189	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	71/262	**0.67(0.46,0.98)**	0.71(0.47,1.08)	0.74(0.50,1.09)	0.92(0.63,1.32)
G:G	39/78	1.24(0.78,1.98)	1.13(0.67,1.91)	1.06(0.82,1.38)	1.07(0.75,1.54)
Log-Add		1.02(0.81,1.30)	0.99(0.76,1.28)	0.99(0.76,1.28)	1.03(0.86,1.25)
Dominant		0.80(0.57,1.13)	0.82(0.56,1.20)	0.83(0.57,1.20)	1.01(0.79,1.29)
Recessive		**1.53(1.00,2.35)**	1.32(0.82,2.13)	1.29(0.82,2.04)	1.00(0.74,1.37)
rs3929					
G:G	131/343	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:G	54/177	0.80(0.55,1.15)	0.83(0.55,1.24)	0.85(0.58,1.26)	0.93(0.68,1.27)
C:C	4/22	0.48(0.16,1.41)	0.40(0.13,1.25)	0.68(0.41,1.13)	0.83(0.35,1.96)
Log-Add		0.76(0.56,1.04)	0.76(0.55,1.07)	0.78(0.56,1.07)	0.92(0.67,1.27)
Dominant		0.76(0.54,1.09)	0.77(0.53,1.14)	0.80(0.55,1.16)	0.90(0.71,1.15)
Recessive		0.51(0.17,1.50)	0.47(0.15,1.44)	0.59(0.26,1.36)	0.63(0.23,1.74)
rs2292305					
T:T	76/247	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	91/212	1.40(0.98,1.99)	1.36(0.92,2.02)	1.33(0.92,1.94)	1.07(0.74,1.56)
C:C	20/66	0.98(0.56,1.73)	0.85(0.46,1.58)	0.92(0.68,1.24)	1.03(0.71,1.49)
Log-Add		1.10(0.86,1.41)	1.05(0.80,1.37)	1.04(0.80,1.35)	1.03(0.87,1.21)
Dominant		1.30(0.93,1.82)	1.23(0.85,1.77)	1.22(0.85,1.74)	1.04(0.82,1.32)
Recessive		0.83(0.49,1.42)	0.76(0.43,1.36)	0.76(0.45,1.30)	0.92(0.62,1.38)

rs2273368					
C:C	64/165	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	78/247	0.81(0.55,1.20)	0.94(0.61,1.44)	0.94(0.63,1.42)	0.99(0.73,1.35)
T:T	42/116	0.93(0.59,1.47)	1.04(0.63,1.73)	1.02(0.80,1.31)	1.00(0.67,1.49)
Log-Add		0.95(0.76,1.20)	1.01(0.79,1.29)	1.01(0.79,1.30)	1.00(0.82,1.21)
Dominant		0.85(0.60,1.22)	0.99(0.67,1.46)	0.98(0.67,1.42)	0.98(0.78,1.24)
Recessive		1.05(0.70,1.57)	1.04(0.67,1.61)	1.07(0.70,1.64)	0.93(0.73,1.20)
rs2953					
T:T	100/310	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
G:T	66/192	1.07(0.74,1.53)	0.90(0.61,1.35)	0.91(0.62,1.33)	0.98(0.74,1.29)
G:G	22/38	**1.80(1.01,3.18)**	**1.91(1.01,3.59)**	**1.36(1.00,1.85)**	1.02(0.64,1.64)
Log-Add		1.23(0.96,1.59)	1.16(0.88,1.53)	1.18(0.89,1.55)	1.00(0.80,1.24)
Dominant		1.19(0.85,1.66)	1.05(0.73,1.51)	1.05(0.74,1.51)	0.94(0.76,1.16)
Recessive		**1.75(1.01,3.05)**	1.81(0.99,3.32)	**1.77(1.01,3.12)**	1.23(0.76,1.99)
Stem Cell Related					
rs6815391					
T:T	83/227	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	71/214	0.91(0.63,1.31)	0.98(0.65,1.47)	0.98(0.66,1.45)	0.92(0.60,1.42)
C:C	27/79	0.93(0.56,1.55)	0.92(0.53,1.60)	0.96(0.73,1.26)	0.90(0.64,1.27)
Log-Add		0.95(0.75,1.21)	0.98(0.75,1.26)	0.96(0.75,1.25)	0.94(0.79,1.14)
Dominant		0.91(0.65,1.29)	0.97(0.67,1.40)	0.96(0.67,1.39)	0.99(0.76,1.29)
Recessive		0.98(0.61,1.57)	0.97(0.58,1.62)	0.94(0.58,1.52)	0.97(0.66,1.42)
rs13409					
C:C	58/185	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	90/247	1.16(0.79,1.70)	1.09(0.72,1.66)	1.09(0.73,1.62)	1.03(0.73,1.46)
T:T	35/103	1.08(0.67,1.76)	0.98(0.57,1.69)	0.99(0.76,1.29)	0.99(0.62,1.59)
Log-Add		1.06(0.83,1.33)	1.00(0.78,1.30)	1.01(0.78,1.30)	1.00(0.80,1.25)
Dominant		1.14(0.80,1.63)	1.07(0.73,1.58)	1.06(0.73,1.54)	0.99(0.82,1.20)
Recessive		0.99(0.65,1.52)	0.92(0.57,1.47)	0.94(0.60,1.48)	0.98(0.72,1.34)
rs3130932					
T:T	87/252	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
G:T	76/215	1.02(0.72,1.46)	1.23(0.83,1.83)	1.21(0.83,1.77)	0.95(0.70,1.29)
G:G	22/68	0.94(0.55,1.61)	1.03(0.57,1.84)	1.01(0.76,1.34)	0.96(0.53,1.76)
Log-Add		0.98(0.77,1.25)	1.06(0.82,1.38)	1.07(0.82,1.38)	0.97(0.74,1.27)
Dominant		1.00(0.72,1.40)	1.15(0.80,1.66)	1.16(0.81,1.66)	0.99(0.75,1.31)
Recessive		0.93(0.56,1.55)	0.94(0.54,1.64)	0.95(0.57,1.59)	0.94(0.64,1.36)
rs2228224					
G:G	102/294	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	66/189	1.01(0.70,1.44)	1.16(0.78,1.73)	1.14(0.78,1.68)	0.91(0.70,1.19)
A:A	11/44	0.72(0.36,1.45)	0.84(0.39,1.78)	0.92(0.64,1.31)	0.89(0.47,1.71)
Log-Add		0.92(0.70,1.20)	1.02(0.76,1.36)	1.01(0.76,1.35)	0.93(0.71,1.23)
Dominant		0.95(0.68,1.34)	1.10(0.76,1.60)	1.09(0.75,1.56)	0.96(0.73,1.26)
Recessive		0.72(0.36,1.42)	0.78(0.37,1.61)	0.83(0.44,1.58)	0.93(0.53,1.64)

rs1126497					
C:C	106/362	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	73/156	**1.60(1.12,2.27)**	**2.17(1.44,3.26)**	**2.04(1.38,3.02)**	1.22(0.91,1.65)
T:T	7/28	0.85(0.36,2.01)	1.03(0.41,2.58)	1.00(0.65,1.55)	0.93(0.56,1.56)
Log-Add		1.26(0.95,1.66)	**1.53(1.13,2.08)**	**1.48(1.09,2.00)**	1.08(0.87,1.34)
Dominant		**1.48(1.06,2.09)**	**2.07(1.40,3.04)**	**1.87(1.29,2.72)**	1.15(0.88,1.51)
Recessive		0.72(0.31,1.69)	0.72(0.29,1.76)	0.85(0.40,1.79)	0.93(0.42,2.04)
rs3740535					
G:G	95/293	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	68/211	0.99(0.69,1.42)	0.84(0.56,1.25)	0.85(0.58,1.24)	0.92(0.71,1.19)
A:A	23/35	**2.03(1.14,3.60)**	1.83(0.96,3.50)	1.33(0.97,1.82)	1.25(0.77,2.03)
Log-Add		1.25(0.96,1.61)	1.13(0.85,1.49)	1.12(0.85,1.48)	1.03(0.83,1.28)
Dominant		1.14(0.82,1.59)	0.99(0.69,1.43)	0.98(0.68,1.40)	0.97(0.76,1.24)
Recessive		**2.03(1.17,3.54)**	**1.86(1.00,3.43)**	1.75(0.99,3.10)	1.07(0.67,1.73)
rs915894					
C:C	51/152	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:C	90/271	0.99(0.67,1.47)	0.97(0.62,1.51)	0.96(0.63,1.47)	1.03(0.81,1.31)
A:A	37/107	1.03(0.63,1.68)	1.20(0.70,2.06)	1.09(0.84,1.42)	1.11(0.79,1.58)
Log-Add		1.01(0.79,1.29)	1.06(0.81,1.38)	1.08(0.83,1.41)	1.05(0.89,1.24)
Dominant		1.00(0.69,1.46)	1.00(0.66,1.51)	1.03(0.69,1.53)	1.01(0.78,1.30)
Recessive		1.04(0.68,1.58)	1.17(0.75,1.85)	1.20(0.78,1.86)	1.02(0.78,1.34)
rs1046472					
C:C	123/350	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:C	60/167	1.02(0.71,1.46)	0.99(0.66,1.47)	0.99(0.67,1.45)	0.97(0.77,1.20)
A:A	6/19	0.90(0.35,2.30)	0.84(0.31,2.28)	0.93(0.58,1.48)	0.92(0.47,1.78)
Log-Add		1.00(0.74,1.34)	0.95(0.69,1.31)	0.96(0.70,1.32)	0.96(0.78,1.18)
Dominant		1.01(0.71,1.43)	0.95(0.65,1.39)	0.97(0.67,1.41)	0.96(0.78,1.20)
Recessive		0.89(0.35,2.27)	0.85(0.32,2.28)	0.90(0.40,1.99)	1.07(0.46,2.53)
rs3734637					
A:A	114/310	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:C	60/191	0.85(0.60,1.23)	0.67(0.45,1.01)	0.70(0.47,1.03)	0.92(0.73,1.16)
C:C	8/35	0.62(0.28,1.38)	0.55(0.23,1.28)	0.76(0.51,1.14)	0.91(0.52,1.59)
Log-Add		0.82(0.62,1.10)	**0.71(0.52,0.97)**	**0.72(0.52,0.98)**	0.94(0.79,1.10)
Dominant		0.82(0.58,1.16)	**0.67(0.46,0.98)**	**0.67(0.47,0.98)**	0.88(0.71,1.09)
Recessive		0.66(0.30,1.45)	0.60(0.26,1.36)	0.71(0.35,1.44)	0.98(0.51,1.88)
rs520692					
A:A	141/396	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	42/124	0.95(0.64,1.42)	0.85(0.55,1.33)	0.87(0.58,1.33)	0.95(0.64,1.42)
G:G	4/17	0.66(0.22,2.00)	0.83(0.25,2.71)	0.92(0.54,1.58)	1.02(0.40,2.56)
Log-Add		0.90(0.65,1.26)	0.89(0.62,1.28)	0.88(0.62,1.26)	0.96(0.69,1.34)
Dominant		0.92(0.62,1.35)	0.87(0.57,1.33)	0.87(0.58,1.30)	0.92(0.70,1.20)
Recessive		0.67(0.22,2.01)	0.89(0.28,2.85)	0.91(0.37,2.22)	1.00(0.35,2.85)
rs8708					
A:A	123/360	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	53/147	1.06(0.73,1.54)	1.09(0.72,1.65)	1.08(0.73,1.61)	0.99(0.68,1.44)

G:G	9/23	1.15(0.52,2.54)	1.51(0.62,3.65)	1.20(0.79,1.84)	1.06(0.55,2.03)
Log-Add		1.06(0.79,1.42)	1.14(0.83,1.57)	1.14(0.83,1.57)	1.00(0.74,1.34)
Dominant		1.07(0.75,1.52)	1.12(0.76,1.65)	1.13(0.77,1.65)	1.02(0.79,1.32)
Recessive		1.13(0.51,2.48)	1.50(0.63,3.55)	1.31(0.62,2.77)	1.17(0.58,2.35)
rs1421					
A:A	121/359	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	61/156	1.16(0.81,1.66)	1.02(0.68,1.53)	1.02(0.69,1.50)	1.00(0.78,1.29)
G:G	5/16	0.93(0.33,2.58)	1.34(0.46,3.89)	1.13(0.69,1.87)	1.40(0.57,3.48)
Log-Add		1.09(0.80,1.48)	1.11(0.79,1.56)	1.06(0.76,1.48)	1.07(0.83,1.37)
Dominant		1.14(0.80,1.62)	1.13(0.77,1.66)	1.04(0.71,1.52)	0.95(0.73,1.25)
Recessive		0.88(0.32,2.45)	1.16(0.40,3.37)	1.19(0.51,2.80)	1.85(0.79,4.32)
rs2269700					
T:T	121/362	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	57/163	1.05(0.73,1.51)	1.04(0.70,1.56)	1.04(0.70,1.53)	0.94(0.68,1.30)
C:C	6/15	1.20(0.45,3.15)	1.22(0.43,3.45)	1.09(0.67,1.78)	0.85(0.44,1.64)
Log-Add		1.06(0.78,1.45)	1.06(0.76,1.49)	1.06(0.76,1.48)	0.94(0.71,1.22)
Dominant		1.06(0.74,1.51)	1.04(0.71,1.53)	1.06(0.72,1.54)	0.94(0.74,1.18)
Recessive		1.18(0.45,3.09)	1.34(0.47,3.82)	1.13(0.49,2.60)	1.38(0.53,3.61)
rs2240308					
G:G	86/252	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	76/203	1.10(0.77,1.57)	0.93(0.61,1.41)	0.93(0.63,1.39)	0.92(0.68,1.26)
A:A	23/46	1.47(0.84,2.56)	1.27(0.68,2.39)	1.12(0.83,1.52)	1.04(0.68,1.58)
Log-Add		1.17(0.91,1.51)	1.08(0.81,1.43)	1.06(0.80,1.40)	0.99(0.81,1.21)
Dominant		1.17(0.83,1.63)	1.02(0.70,1.50)	1.00(0.68,1.45)	1.06(0.77,1.46)
Recessive		1.40(0.83,2.39)	1.33(0.73,2.41)	1.26(0.72,2.19)	1.14(0.66,1.96)
rs3729629					
G:G	92/236	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:G	75/233	0.83(0.58,1.18)	0.69(0.46,1.03)	0.71(0.49,1.04)	0.87(0.68,1.10)
C:C	20/66	0.78(0.45,1.35)	0.76(0.41,1.41)	0.89(0.66,1.19)	0.95(0.61,1.48)
Log-Add		0.86(0.67,1.11)	0.83(0.63,1.09)	0.81(0.62,1.07)	0.94(0.78,1.13)
Dominant		0.82(0.58,1.14)	0.71(0.49,1.02)	0.72(0.50,1.03)	0.89(0.70,1.13)
Recessive		0.85(0.50,1.45)	1.00(0.56,1.77)	0.92(0.54,1.58)	0.97(0.69,1.38)
rs4730775					
C:C	96/307	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	74/182	1.30(0.91,1.85)	1.11(0.75,1.65)	1.11(0.76,1.62)	0.98(0.71,1.35)
T:T	16/42	1.22(0.66,2.26)	1.25(0.63,2.46)	1.10(0.80,1.54)	1.12(0.73,1.72)
Log-Add		1.18(0.91,1.52)	1.11(0.84,1.47)	1.11(0.84,1.47)	1.02(0.85,1.23)
Dominant		1.28(0.92,1.80)	1.14(0.79,1.64)	1.13(0.79,1.62)	1.01(0.77,1.32)
Recessive		1.10(0.60,2.00)	1.16(0.61,2.24)	1.15(0.63,2.09)	1.05(0.67,1.66)
rs4835761					
A:A	65/175	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	82/237	0.93(0.64,1.36)	0.89(0.59,1.36)	0.90(0.60,1.35)	0.92(0.69,1.22)
G:G	38/98	1.04(0.65,1.67)	1.03(0.61,1.74)	1.02(0.79,1.31)	0.93(0.63,1.38)
Log-Add		1.01(0.80,1.28)	0.96(0.74,1.24)	1.00(0.78,1.29)	0.96(0.79,1.15)
Dominant		0.96(0.68,1.37)	0.87(0.59,1.27)	0.94(0.65,1.37)	1.01(0.77,1.32)

Recessive		1.09(0.71,1.65)	1.08(0.68,1.70)	1.09(0.70,1.69)	0.95(0.74,1.22)
rs2241802					
G:G	66/159	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	89/243	0.88(0.61,1.29)	0.98(0.65,1.50)	0.99(0.66,1.47)	0.96(0.74,1.25)
A:A	33/115	0.69(0.43,1.12)	0.87(0.51,1.49)	0.93(0.72,1.21)	0.90(0.64,1.27)
Log-Add		0.84(0.66,1.06)	0.91(0.70,1.17)	0.94(0.73,1.22)	0.95(0.80,1.11)
Dominant		0.82(0.58,1.17)	0.88(0.60,1.30)	0.95(0.65,1.39)	0.96(0.73,1.26)
Recessive		0.74(0.48,1.14)	0.86(0.54,1.38)	0.89(0.57,1.40)	0.94(0.68,1.29)
rs222851					
A:A	70/219	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	90/234	1.20(0.84,1.73)	1.23(0.82,1.84)	1.21(0.82,1.78)	0.98(0.75,1.28)
G:G	25/72	1.09(0.64,1.84)	1.19(0.66,2.13)	1.08(0.81,1.44)	0.97(0.65,1.44)
Log-Add		1.08(0.85,1.38)	1.11(0.85,1.45)	1.12(0.86,1.46)	0.98(0.81,1.18)
Dominant		1.18(0.83,1.66)	1.18(0.81,1.72)	1.20(0.83,1.74)	1.02(0.80,1.30)
Recessive		0.98(0.60,1.60)	1.07(0.63,1.82)	1.05(0.63,1.73)	1.02(0.68,1.52)
rs1981492					
G:G	103/274	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	65/206	0.84(0.59,1.20)	0.79(0.53,1.18)	0.81(0.55,1.19)	0.90(0.71,1.15)
A:A	14/46	0.81(0.43,1.53)	0.83(0.41,1.71)	0.92(0.65,1.30)	0.96(0.65,1.42)
Log-Add		0.87(0.67,1.14)	0.86(0.65,1.16)	0.86(0.65,1.16)	0.95(0.80,1.14)
Dominant		0.83(0.59,1.17)	0.81(0.56,1.17)	0.81(0.57,1.17)	0.97(0.69,1.37)
Recessive		0.87(0.47,1.62)	0.93(0.47,1.84)	0.93(0.50,1.73)	0.98(0.54,1.79)
rs6754757					
T:T	113/311	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
G:T	65/153	1.17(0.81,1.68)	1.07(0.71,1.63)	1.07(0.72,1.59)	1.03(0.83,1.28)
G:G	9/38	0.65(0.31,1.39)	0.79(0.34,1.86)	0.90(0.60,1.34)	0.83(0.48,1.44)
Log-Add		0.97(0.74,1.27)	0.92(0.67,1.26)	0.98(0.72,1.33)	0.96(0.79,1.16)
Dominant		1.07(0.76,1.50)	0.99(0.67,1.46)	1.02(0.70,1.50)	0.99(0.74,1.33)
Recessive		0.62(0.29,1.30)	0.61(0.26,1.43)	0.82(0.40,1.68)	0.97(0.56,1.67)
HIF-1α pathway					
rs2295778					
C:C	104/304	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:G	65/169	1.12(0.78,1.62)	1.07(0.70,1.62)	1.06(0.71,1.58)	0.94(0.72,1.22)
G:G	14/29	1.41(0.72,2.77)	1.35(0.62,2.94)	1.15(0.79,1.67)	0.97(0.58,1.64)
Log-Add		1.16(0.88,1.52)	1.09(0.80,1.48)	1.11(0.82,1.51)	0.97(0.78,1.21)
Dominant		1.17(0.83,1.64)	1.08(0.73,1.59)	1.10(0.76,1.61)	0.98(0.73,1.30)
Recessive		1.35(0.70,2.62)	1.25(0.59,2.65)	1.24(0.63,2.42)	1.07(0.61,1.86)
rs2057482					
C:C	124/340	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
T:C	58/157	1.01(0.70,1.46)	1.04(0.70,1.56)	1.04(0.71,1.53)	0.92(0.64,1.31)
T:T	8/28	0.78(0.35,1.76)	0.73(0.30,1.80)	0.87(0.56,1.33)	0.82(0.34,1.98)
Log-Add		0.95(0.72,1.27)	0.91(0.66,1.25)	0.95(0.70,1.30)	0.92(0.71,1.19)
Dominant		0.98(0.69,1.39)	0.94(0.64,1.38)	0.99(0.68,1.44)	1.02(0.82,1.28)

Recessive		0.78(0.35,1.74)	0.68(0.28,1.66)	0.79(0.38,1.66)	1.04(0.54,2.00)
NFKB Pathway					
rs2230793					
A:A	101/240	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:C	68/238	**0.68(0.48,0.97)**	**0.62(0.42,0.92)**	**0.65(0.44,0.94)**	0.88(0.66,1.16)
C:C	18/53	0.81(0.45,1.45)	0.83(0.44,1.57)	0.92(0.68,1.25)	0.92(0.54,1.54)
Log-Add		0.80(0.62,1.04)	0.80(0.60,1.06)	0.80(0.60,1.05)	0.92(0.72,1.19)
Dominant		**0.70(0.50,0.98)**	**0.68(0.47,0.98)**	**0.68(0.47,0.97)**	0.90(0.70,1.16)
Recessive		0.96(0.55,1.69)	1.01(0.55,1.85)	1.02(0.58,1.78)	1.06(0.68,1.66)
rs1538660					
C:C	85/235	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	81/238	0.94(0.66,1.34)	0.88(0.59,1.30)	0.88(0.61,1.29)	0.97(0.67,1.41)
T:T	21/55	1.06(0.60,1.85)	1.01(0.54,1.88)	1.01(0.74,1.36)	0.95(0.60,1.52)
Log-Add		1.00(0.77,1.28)	0.95(0.72,1.25)	0.96(0.73,1.26)	0.97(0.78,1.22)
Dominant		0.96(0.69,1.35)	0.89(0.62,1.28)	0.91(0.63,1.30)	0.99(0.78,1.25)
Recessive		1.09(0.64,1.85)	1.07(0.60,1.93)	1.06(0.62,1.83)	1.10(0.72,1.68)
rs12894467					
T:T	100/338	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	76/158	**1.63(1.14,2.31)**	**1.76(1.19,2.60)**	**1.69(1.16,2.46)**	1.05(0.81,1.37)
C:C	7/26	0.91(0.38,2.16)	1.18(0.46,3.05)	1.07(0.68,1.67)	1.01(0.48,2.13)
Log-Add		1.29(0.98,1.71)	**1.42(1.04,1.94)**	**1.41(1.04,1.92)**	1.04(0.79,1.35)
Dominant		**1.52(1.08,2.15)**	**1.66(1.14,2.41)**	**1.63(1.13,2.35)**	1.09(0.86,1.39)
Recessive		0.76(0.32,1.78)	0.95(0.37,2.44)	0.96(0.45,2.09)	1.10(0.63,1.95)
rs8904					
C:C	72/205	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	80/233	0.98(0.68,1.41)	0.95(0.63,1.44)	0.95(0.64,1.41)	1.05(0.83,1.31)
T:T	35/95	1.05(0.65,1.68)	1.13(0.67,1.89)	1.06(0.83,1.37)	1.06(0.74,1.52)
Log-Add		1.02(0.81,1.28)	1.06(0.83,1.37)	1.04(0.81,1.34)	1.03(0.88,1.21)
Dominant		1.00(0.71,1.41)	1.04(0.71,1.51)	1.00(0.69,1.44)	0.98(0.77,1.25)
Recessive		1.06(0.69,1.63)	1.17(0.74,1.86)	1.15(0.74,1.79)	1.05(0.79,1.39)

Notation: Age (continuous variable), BMI categories, tobacco smoking status, pack-years of smoking, and county of residence were the covariates adjusted for in all multivariable logistic regression models.

Table 3-8. Candidate SNPs and risk of lung cancer in post-menopausal women in Jiangsu Study, grouped by parity

	All	Parity<=3					Parity>=4				
dbSNP no.	ca/co	ca/co	cOR	aOR	sbOR	miOR	ca/co	cOR	aOR	sbOR	miOR
Total	191/564	102/265					89/299				
Micro RNA Related											
rs1804429											
T:T	164/459	91/213	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	73/246	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
G:T	23/72	9/35	0.60(0.28,1.30)	0.64(0.27,1.49)	0.71(0.35,1.45)	0.94(0.62,1.44)	14/37	1.28(0.65,2.49)	1.20(0.55,2.61)	1.14(0.58,2.26)	1.05(0.51,2.16)
G:G	0/2	0/2	0.00(0.00,I)	0.00(0.00,I)	0.81(0.25,2.68)	NA	0/0	NA	NA	NA	NA
Log-Add			0.56(0.27,1.18)	0.59(0.26,1.33)	0.68(0.34,1.37)	0.93(0.62,1.39)		1.28(0.65,2.49)	1.18(0.55,2.55)	1.14(0.58,2.26)	0.98(0.55,1.75)
Dominant			0.57(0.26,1.23)	0.60(0.26,1.37)	0.69(0.34,1.41)	0.96(0.61,1.50)		1.28(0.65,2.49)	1.18(0.55,2.55)	1.14(0.58,2.26)	0.98(0.55,1.75)
Recessive			0.00(0.00,I)	0.00(0.00,I)	0.88(0.24,3.30)	NA		NA	NA	NA	
rs10519613											
C:C	66/190	32/92	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	34/98	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:A	88/241	52/110	1.36(0.81,2.29)	1.28(0.72,2.27)	1.25(0.74,2.12)	1.00(0.71,1.41)	36/131	0.79(0.46,1.35)	0.57(0.31,1.06)	0.63(0.36,1.11)	0.77(0.42,1.40)
A:A	29/97	16/46	1.00(0.50,2.01)	0.83(0.38,1.84)	0.93(0.64,1.34)	0.99(0.55,1.79)	13/51	0.73(0.36,1.51)	0.51(0.22,1.18)	0.75(0.51,1.11)	0.76(0.35,1.62)
Log-Add			1.05(0.76,1.46)	1.00(0.70,1.44)	0.99(0.70,1.42)	1.00(0.74,1.34)		0.84(0.59,1.20)	0.70(0.47,1.05)	0.70(0.48,1.04)	0.86(0.57,1.29)
Dominant			1.25(0.77,2.05)	1.19(0.69,2.03)	1.15(0.69,1.90)	0.95(0.63,1.43)		0.78(0.47,1.28)	0.57(0.32,1.02)	0.60(0.35,1.03)	0.90(0.66,1.24)
Recessive			0.84(0.45,1.56)	0.76(0.38,1.52)	0.79(0.42,1.48)	0.87(0.59,1.29)		0.83(0.43,1.62)	0.74(0.35,1.56)	0.76(0.40,1.47)	0.88(0.48,1.65)
rs12828											
G:G	79/208	46/108	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	33/100	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	74/240	38/107	0.83(0.50,1.38)	0.69(0.38,1.24)	0.72(0.42,1.23)	0.84(0.54,1.30)	36/133	0.82(0.48,1.41)	0.66(0.36,1.22)	0.71(0.41,1.24)	0.89(0.58,1.35)
A:A	28/77	15/35	1.01(0.50,2.02)	1.14(0.52,2.50)	1.07(0.74,1.55)	0.84(0.50,1.42)	13/42	0.94(0.45,1.96)	0.78(0.34,1.79)	0.91(0.61,1.34)	0.90(0.42,1.90)
Log-Add			0.96(0.69,1.34)	0.99(0.68,1.44)	0.96(0.66,1.38)	0.91(0.72,1.15)		0.93(0.65,1.33)	0.83(0.55,1.24)	0.84(0.57,1.24)	0.93(0.69,1.27)
Dominant			0.88(0.55,1.40)	0.86(0.51,1.45)	0.81(0.49,1.33)	0.88(0.63,1.25)		0.85(0.51,1.41)	0.67(0.38,1.19)	0.73(0.43,1.23)	0.89(0.63,1.26)
Recessive			1.10(0.57,2.11)	1.30(0.63,2.69)	1.26(0.66,2.42)	1.00(0.60,1.66)		1.05(0.53,2.06)	1.01(0.47,2.19)	0.98(0.50,1.91)	0.98(0.48,2.03)
rs896849											
T:T	147/402	79/191	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	68/211	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
T:C	32/117	19/50	0.92(0.51,1.66)	0.79(0.41,1.52)	0.82(0.46,1.48)	0.84(0.49,1.45)	13/67	0.60(0.31,1.16)	0.67(0.32,1.40)	0.73(0.38,1.38)	0.88(0.54,1.41)
C:C	7/14	2/9	0.54(0.11,2.54)	0.56(0.10,3.09)	0.80(0.40,1.63)	0.87(0.21,3.60)	5/5	3.10(0.87,11.04	2.34(0.53,10.40	1.40(0.73,2.70)	2.03(0.38,10.93
Log-Add			0.84(0.52,1.36)	0.77(0.45,1.30)	0.79(0.48,1.30)	0.86(0.52,1.44)		0.98(0.61,1.59)	0.98(0.58,1.68)	0.99(0.60,1.64)	0.99(0.65,1.51)
Dominant			0.86(0.49,1.51)	0.75(0.40,1.38)	0.79(0.45,1.39)	0.94(0.69,1.29)		0.78(0.43,1.39)	0.82(0.43,1.59)	0.85(0.47,1.55)	0.90(0.52,1.54)
Recessive			0.55(0.12,2.57)	0.59(0.11,3.20)	0.79(0.28,2.24)	1.33(0.37,4.81)		3.43(0.97,12.15	2.42(0.56,10.50	1.55(0.56,4.26)	3.37(0.84,13.53
rs11614913											
T:T	55/159	30/72	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	25/87	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	82/253	43/120	0.86(0.50,1.49)	0.78(0.41,1.47)	0.81(0.46,1.43)	0.88(0.59,1.31)	39/133	1.02(0.58,1.80)	1.06(0.56,2.03)	1.05(0.59,1.88)	1.14(0.71,1.83)
C:C	44/112	26/53	1.18(0.62,2.22)	1.43(0.70,2.93)	1.21(0.86,1.70)	0.96(0.53,1.77)	18/59	1.06(0.53,2.12)	1.10(0.51,2.38)	1.04(0.72,1.50)	1.35(0.67,2.74)
Log-Add			1.07(0.78,1.48)	1.08(0.76,1.55)	1.18(0.83,1.68)	0.99(0.73,1.34)		1.03(0.73,1.45)	1.03(0.71,1.52)	1.04(0.72,1.51)	1.16(0.81,1.67)

Dominant			0.96(0.58,1.59)	0.91(0.52,1.61)	0.98(0.58,1.68)	0.96(0.66,1.38)		1.03(0.61,1.76)	1.05(0.57,1.90)	1.06(0.61,1.84)	1.05(0.63,1.76)
Recessive			1.29(0.75,2.22)	1.39(0.77,2.51)	1.55(0.89,2.72)	1.15(0.70,1.89)		1.05(0.58,1.90)	1.05(0.54,2.05)	1.05(0.57,1.91)	0.96(0.55,1.67)
rs2910164											
C:C	64/206	35/87	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	29/119	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
G:C	80/236	45/120	0.93(0.55,1.57)	1.02(0.57,1.82)	1.02(0.60,1.74)	0.97(0.65,1.45)	35/116	1.24(0.71,2.16)	1.29(0.68,2.44)	1.21(0.68,2.15)	1.05(0.67,1.66)
G:G	40/91	19/44	1.07(0.55,2.09)	1.28(0.61,2.68)	1.13(0.79,1.60)	0.94(0.62,1.42)	21/47	1.83(0.95,3.53)	**2.62(1.22,5.59)**	**1.55(1.08,2.22)**	1.49(0.63,3.52)
Log-Add			1.02(0.73,1.42)	1.11(0.78,1.59)	1.12(0.78,1.59)	0.97(0.79,1.19)		1.34(0.97,1.86)	**1.57(1.07,2.29)**	**1.53(1.06,2.20)**	1.17(0.83,1.66)
Dominant			0.97(0.60,1.58)	1.08(0.63,1.85)	1.09(0.65,1.80)	0.97(0.69,1.34)		1.41(0.85,2.34)	1.60(0.90,2.85)	1.51(0.89,2.58)	1.19(0.74,1.93)
Recessive			1.12(0.62,2.03)	1.27(0.67,2.41)	1.22(0.67,2.21)	1.03(0.70,1.51)		1.64(0.92,2.94)	**2.31(1.17,4.56)**	**1.95(1.06,3.61)**	1.26(0.74,2.14)
rs895819											
T:T	100/287	61/137	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	39/150	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
T:C	71/203	32/93	0.77(0.47,1.28)	0.85(0.49,1.48)	0.88(0.53,1.48)	0.88(0.61,1.27)	39/110	1.36(0.82,2.27)	1.24(0.70,2.21)	1.20(0.71,2.04)	1.06(0.63,1.78)
C:C	15/47	8/22	0.82(0.34,1.94)	0.77(0.30,1.98)	0.89(0.57,1.40)	0.96(0.49,1.85)	7/25	1.08(0.43,2.67)	1.26(0.46,3.47)	1.10(0.69,1.77)	1.04(0.51,2.13)
Log-Add			0.85(0.59,1.22)	0.89(0.60,1.32)	0.88(0.60,1.29)	0.96(0.71,1.28)		1.16(0.80,1.68)	1.13(0.74,1.73)	1.15(0.77,1.73)	1.03(0.74,1.42)
Dominant			0.78(0.49,1.25)	0.86(0.52,1.44)	0.86(0.53,1.40)	0.94(0.66,1.33)		1.31(0.81,2.13)	1.20(0.69,2.08)	1.21(0.73,2.01)	1.04(0.57,1.90)
Recessive			0.90(0.39,2.09)	0.84(0.34,2.12)	0.87(0.40,1.87)	0.90(0.45,1.81)		0.93(0.39,2.24)	1.09(0.41,2.85)	1.09(0.49,2.42)	0.93(0.45,1.92)
rs7372209											
C:C	94/276	47/138	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	47/138	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	71/224	43/96	1.32(0.81,2.14)	1.38(0.80,2.36)	1.31(0.79,2.15)	0.95(0.63,1.41)	28/128	0.64(0.38,1.09)	0.63(0.35,1.15)	0.67(0.39,1.15)	0.92(0.64,1.31)
T:T	19/35	10/19	1.55(0.67,3.56)	1.59(0.62,4.04)	1.21(0.78,1.87)	0.95(0.49,1.83)	9/16	1.65(0.68,3.99)	2.05(0.73,5.76)	1.39(0.86,2.25)	1.52(0.42,5.51)
Log-Add			1.27(0.89,1.81)	1.37(0.93,2.02)	1.27(0.87,1.85)	0.97(0.71,1.32)		0.95(0.64,1.41)	1.01(0.65,1.58)	1.00(0.65,1.52)	1.05(0.76,1.47)
Dominant			1.35(0.85,2.15)	1.44(0.87,2.38)	1.34(0.83,2.17)	1.05(0.75,1.46)		0.75(0.46,1.23)	0.78(0.44,1.35)	0.79(0.47,1.33)	0.99(0.70,1.41)
Recessive			1.37(0.61,3.06)	1.65(0.69,3.96)	1.23(0.58,2.63)	1.09(0.67,1.76)		2.00(0.85,4.70)	2.50(0.94,6.63)	1.82(0.80,4.14)	1.43(0.44,4.66)
rs3742330											
A:A	74/235	39/108	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	35/127	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	82/224	41/107	1.06(0.63,1.77)	0.97(0.55,1.73)	0.99(0.58,1.67)	0.94(0.68,1.29)	41/117	1.27(0.76,2.13)	1.09(0.61,1.96)	1.08(0.63,1.85)	1.05(0.73,1.51)
G:G	30/80	21/37	1.57(0.82,3.01)	1.70(0.82,3.52)	1.28(0.90,1.81)	0.95(0.55,1.64)	9/43	0.76(0.34,1.71)	0.74(0.29,1.87)	0.87(0.57,1.35)	0.86(0.40,1.88)
Log-Add			1.22(0.89,1.68)	1.23(0.87,1.75)	1.22(0.86,1.73)	0.97(0.76,1.23)		0.97(0.69,1.38)	0.93(0.62,1.39)	0.94(0.64,1.38)	0.97(0.71,1.33)
Dominant			1.19(0.74,1.91)	1.21(0.72,2.02)	1.14(0.70,1.86)	0.98(0.73,1.33)		1.13(0.69,1.85)	1.02(0.59,1.77)	1.00(0.60,1.68)	0.97(0.67,1.41)
Recessive			1.53(0.84,2.76)	1.57(0.82,3.02)	1.53(0.83,2.81)	1.08(0.66,1.77)		0.67(0.31,1.44)	0.68(0.28,1.65)	0.79(0.38,1.64)	0.86(0.44,1.68)
rs4961280											
C:C	157/412	83/193	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	74/219	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:A	29/98	17/45	0.88(0.48,1.62)	0.68(0.34,1.37)	0.75(0.41,1.39)	0.84(0.60,1.18)	12/53	0.67(0.34,1.32)	0.87(0.41,1.85)	0.91(0.47,1.76)	0.97(0.58,1.64)
A:A	1/10	1/5	0.47(0.05,4.04)	0.29(0.03,2.87)	0.68(0.30,1.55)	0.54(0.08,3.57)	0/5	0.00(0.00,I)	0.00(0.00,I)	0.62(0.22,1.74)	NA
Log-Add			0.82(0.48,1.41)	0.73(0.40,1.31)	0.69(0.40,1.19)	0.83(0.62,1.11)		0.59(0.31,1.12)	0.71(0.36,1.41)	0.78(0.43,1.43)	0.92(0.56,1.51)
Dominant			0.84(0.46,1.52)	0.73(0.38,1.40)	0.70(0.38,1.28)	0.97(0.50,1.86)		0.61(0.31,1.20)	0.76(0.36,1.58)	0.83(0.44,1.59)	0.99(0.52,1.86)
Recessive			0.48(0.05,4.13)	0.42(0.04,3.99)	0.70(0.23,2.16)	0.42(0.04,3.89)		0.00(0.00,I)	0.00(0.00,I)	0.69(0.20,2.33)	NA
rs14035											
C:C	140/355	74/169	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	66/186	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	42/127	26/61	0.97(0.57,1.66)	0.93(0.51,1.69)	0.94(0.55,1.63)	0.90(0.54,1.51)	16/66	0.68(0.37,1.26)	0.86(0.42,1.74)	0.89(0.48,1.67)	0.87(0.49,1.55)
T:T	5/26	1/10	0.23(0.03,1.82)	0.32(0.04,2.76)	0.68(0.31,1.50)	0.74(0.18,3.09)	4/16	0.70(0.23,2.18)	0.94(0.25,3.51)	0.98(0.54,1.77)	1.00(0.34,2.97)

Log-Add			0.80(0.51,1.26)	0.89(0.54,1.48)	0.83(0.51,1.35)	0.90(0.57,1.43)		0.76(0.49,1.19)	0.90(0.54,1.50)	0.93(0.58,1.50)	0.92(0.65,1.32)
Dominant			0.87(0.52,1.46)	0.97(0.54,1.71)	0.87(0.51,1.50)	0.92(0.65,1.30)		0.69(0.39,1.21)	0.85(0.45,1.62)	0.90(0.50,1.62)	0.92(0.58,1.48)
Recessive			0.23(0.03,1.82)	0.35(0.04,2.91)	0.67(0.23,1.98)	0.35(0.04,2.96)		0.77(0.25,2.36)	0.96(0.26,3.54)	0.99(0.38,2.56)	0.99(0.34,2.84)
rs197412											
T:T	93/237	41/116	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	52/121	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
T:C	66/238	42/104	1.14(0.69,1.89)	1.39(0.79,2.44)	1.31(0.78,2.20)	1.03(0.78,1.36)	24/134	**0.42(0.24,0.72)**	**0.41(0.22,0.76)**	**0.48(0.28,0.83)**	0.76(0.50,1.15)
C:C	26/56	16/28	1.62(0.79,3.29)	1.81(0.82,4.00)	1.29(0.89,1.88)	1.07(0.66,1.73)	10/28	0.83(0.38,1.83)	0.84(0.34,2.06)	0.95(0.62,1.45)	0.89(0.38,2.07)
Log-Add			1.24(0.89,1.73)	1.27(0.89,1.81)	1.32(0.92,1.88)	1.04(0.84,1.28)		0.68(0.46,1.00)	0.68(0.45,1.04)	0.72(0.48,1.07)	0.87(0.64,1.19)
Dominant			1.24(0.78,1.99)	1.38(0.83,2.30)	1.40(0.86,2.29)	1.03(0.71,1.48)		**0.49(0.30,0.80)**	**0.48(0.28,0.84)**	**0.54(0.32,0.90)**	0.83(0.48,1.44)
Recessive			1.51(0.78,2.94)	1.37(0.67,2.80)	1.39(0.72,2.67)	1.04(0.59,1.82)		1.20(0.56,2.58)	1.20(0.50,2.85)	1.15(0.55,2.41)	1.12(0.59,2.13)
rs2740348											
G:G	144/412	77/180	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	67/232	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
G:C	32/91	18/52	0.81(0.44,1.47)	0.82(0.42,1.60)	0.86(0.47,1.57)	0.86(0.51,1.45)	14/39	1.24(0.64,2.43)	1.63(0.77,3.47)	1.46(0.75,2.85)	1.04(0.66,1.62)
C:C	4/13	3/9	0.78(0.21,2.96)	0.95(0.22,4.05)	0.99(0.52,1.88)	0.81(0.30,2.19)	1/4	0.87(0.10,7.88)	0.54(0.05,5.99)	0.83(0.34,2.01)	0.71(0.07,7.25)
Log-Add			0.84(0.53,1.34)	0.84(0.51,1.41)	0.91(0.56,1.48)	0.87(0.56,1.35)		1.14(0.65,2.03)	1.28(0.67,2.42)	1.22(0.68,2.19)	1.01(0.68,1.50)
Dominant			0.80(0.46,1.41)	0.80(0.43,1.48)	0.88(0.49,1.55)	1.01(0.67,1.52)		1.21(0.63,2.31)	1.48(0.72,3.04)	1.36(0.71,2.60)	1.01(0.65,1.59)
Recessive			0.81(0.22,3.07)	0.87(0.21,3.57)	1.01(0.37,2.74)	0.93(0.15,5.93)		0.84(0.09,7.59)	0.50(0.04,5.56)	0.83(0.26,2.69)	0.67(0.07,6.93)
rs7813											
T:T	89/266	46/113	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	43/153	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	71/189	43/94	1.12(0.68,1.85)	1.15(0.66,2.00)	1.14(0.69,1.91)	0.92(0.68,1.26)	28/95	1.05(0.61,1.80)	1.42(0.77,2.63)	1.34(0.77,2.35)	1.13(0.72,1.79)
C:C	18/58	8/33	0.60(0.26,1.39)	0.62(0.25,1.57)	0.81(0.52,1.25)	0.76(0.40,1.43)	10/25	1.42(0.63,3.19)	1.70(0.67,4.31)	1.26(0.81,1.96)	1.38(0.61,3.11)
Log-Add			0.88(0.62,1.25)	0.86(0.59,1.25)	0.91(0.63,1.32)	0.89(0.69,1.16)		1.14(0.79,1.65)	1.34(0.89,2.02)	1.31(0.89,1.95)	1.18(0.88,1.58)
Dominant			0.99(0.62,1.58)	0.96(0.57,1.61)	1.02(0.63,1.67)	0.94(0.67,1.32)		1.13(0.69,1.85)	1.47(0.83,2.59)	1.41(0.84,2.38)	0.97(0.65,1.45)
Recessive			0.56(0.25,1.27)	0.53(0.22,1.27)	0.68(0.33,1.42)	0.89(0.54,1.49)		1.40(0.64,3.05)	1.52(0.62,3.69)	1.33(0.62,2.83)	1.01(0.44,2.32)
rs11077											
A:A	165/466	88/214	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	77/252	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:C	22/64	12/33	0.88(0.44,1.79)	0.84(0.38,1.87)	0.87(0.44,1.74)	0.85(0.50,1.44)	10/31	1.06(0.50,2.25)	0.77(0.32,1.89)	0.83(0.39,1.75)	0.97(0.48,1.99)
C:C	1/5	1/4	0.61(0.07,5.52)	0.45(0.04,4.94)	0.79(0.33,1.88)	0.68(0.09,5.51)	0/1	0.00(0.00,I)	0.00(0.00,I)	0.89(0.25,3.17)	0.11(0.00,5.884
Log-Add			0.85(0.47,1.55)	0.78(0.40,1.51)	0.81(0.45,1.47)	0.86(0.55,1.34)		0.99(0.47,2.06)	0.73(0.31,1.73)	0.81(0.39,1.67)	1.00(0.48,2.06)
Dominant			0.85(0.43,1.68)	0.77(0.37,1.63)	0.83(0.43,1.61)	0.93(0.50,1.75)		1.02(0.48,2.18)	0.74(0.31,1.77)	0.82(0.39,1.71)	0.91(0.48,1.72)
Recessive			0.62(0.07,5.59)	0.52(0.04,6.11)	0.80(0.25,2.57)	0.71(0.07,7.20)		0.00(0.00,I)	0.00(0.00,I)	0.94(0.24,3.61)	NA
rs9266											
C:C	124/356	63/169	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	61/187	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	56/154	33/68	1.30(0.78,2.16)	1.03(0.58,1.82)	1.04(0.62,1.77)	0.92(0.61,1.38)	23/86	0.82(0.48,1.41)	0.62(0.33,1.16)	0.67(0.38,1.18)	0.86(0.58,1.28)
T:T	10/26	5/15	0.89(0.31,2.56)	0.56(0.17,1.87)	0.78(0.45,1.34)	0.82(0.43,1.55)	5/11	1.39(0.47,4.17)	1.94(0.57,6.62)	1.34(0.76,2.36)	1.25(0.31,5.05)
Log-Add			1.11(0.76,1.63)	0.92(0.60,1.41)	0.89(0.59,1.35)	0.92(0.67,1.25)		0.97(0.64,1.48)	0.89(0.54,1.45)	0.91(0.57,1.45)	0.92(0.66,1.30)
Dominant			1.23(0.76,1.99)	0.96(0.57,1.64)	0.95(0.58,1.58)	0.93(0.66,1.33)		0.88(0.53,1.47)	0.72(0.40,1.30)	0.77(0.45,1.32)	0.92(0.64,1.32)
Recessive			0.82(0.29,2.33)	0.65(0.20,2.10)	0.70(0.29,1.68)	0.85(0.49,1.48)		1.48(0.50,4.37)	2.25(0.67,7.59)	1.57(0.62,4.02)	2.02(0.60,6.76)
rs4072391											
C:C	156/439	83/204	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	73/235	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	27/92	15/43	0.86(0.45,1.63)	1.08(0.53,2.20)	1.06(0.57,2.00)	0.87(0.59,1.28)	12/49	0.79(0.40,1.56)	1.11(0.51,2.45)	1.08(0.54,2.15)	0.95(0.49,1.82)

T:T	3/6	2/5	0.98(0.19,5.17)	1.77(0.30,10.55	1.22(0.57,2.64)	1.34(0.27,6.67)	1/1	3.22(0.20,52.11)	3.49(0.17,70.89)	1.33(0.47,3.74)	0.82(0.21,3.27)
Log-Add			0.90(0.53,1.53)	1.09(0.62,1.92)	1.14(0.67,1.96)	0.90(0.62,1.31)		0.90(0.48,1.68)	1.18(0.58,2.38)	1.18(0.63,2.22)	0.95(0.57,1.57)
Dominant			0.87(0.47,1.60)	1.07(0.55,2.06)	1.12(0.61,2.05)	0.97(0.68,1.40)		0.84(0.43,1.63)	1.12(0.52,2.40)	1.14(0.58,2.23)	0.93(0.52,1.65)
Recessive			1.01(0.19,5.28)	1.46(0.26,8.11)	1.22(0.40,3.76)	1.78(0.36,8.78)		3.34(0.21,53.98)	3.60(0.18,73.34)	1.23(0.34,4.41)	4.99(0.29,84.93
rs42031											
A:A	180/484	96/233	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	84/251	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:T	9/53	5/17	0.71(0.26,1.99)	1.01(0.32,3.20)	1.01(0.41,2.44)	0.94(0.55,1.60)	4/36	0.33(0.11,0.96)	0.32(0.10,1.02)	0.50(0.22,1.15)	1.00(ref)
T:T	0/4	0/4	0.00(0.00,I)	0.00(0.00,I)	0.53(0.20,1.43)	0.73(0.08,7.06)	0/0	NA	NA	NA	NA
Log-Add			0.55(0.22,1.37)	0.55(0.21,1.43)	0.68(0.32,1.44)	0.93(0.57,1.52)		**0.33(0.11,0.96)**	**0.31(0.10,0.98)**	0.50(0.22,1.15)	0.67(0.19,2.34)
Dominant			0.58(0.21,1.58)	0.59(0.20,1.73)	0.78(0.33,1.81)	0.93(0.60,1.45)		**0.33(0.11,0.96)**	**0.31(0.10,0.98)**	0.50(0.22,1.15)	0.67(0.19,2.34)
Recessive			0.00(0.00,I)	0.00(0.00,I)	0.59(0.18,1.96)	0.73(0.08,7.08)		NA	NA	NA	
rs2075993											
G:G	75/192	34/87	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	41/105	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
G:A	76/237	44/113	1.00(0.59,1.69)	1.01(0.56,1.82)	1.01(0.59,1.73)	0.98(0.66,1.45)	32/124	0.66(0.39,1.12)	0.66(0.36,1.22)	0.71(0.41,1.24)	0.91(0.46,1.81)
A:A	28/84	16/37	1.11(0.55,2.25)	0.81(0.35,1.84)	0.91(0.61,1.34)	0.94(0.44,2.03)	12/47	0.65(0.32,1.36)	0.61(0.26,1.39)	0.81(0.54,1.20)	0.86(0.38,1.96)
Log-Add			1.04(0.74,1.47)	0.99(0.68,1.45)	0.93(0.64,1.35)	0.98(0.68,1.40)		0.77(0.54,1.09)	0.75(0.50,1.10)	0.77(0.52,1.12)	0.93(0.60,1.45)
Dominant			1.02(0.62,1.68)	1.03(0.60,1.77)	0.96(0.57,1.61)	1.05(0.73,1.50)		0.66(0.40,1.08)	0.65(0.37,1.14)	0.69(0.41,1.15)	0.89(0.58,1.37)
Recessive			1.11(0.58,2.11)	0.93(0.45,1.92)	0.84(0.44,1.63)	0.98(0.69,1.37)		0.80(0.40,1.59)	0.71(0.33,1.56)	0.80(0.41,1.57)	0.94(0.59,1.48)
rs3801790											
A:A	76/189	40/81	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	36/108	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	71/262	42/131	0.65(0.39,1.09)	0.69(0.39,1.23)	0.75(0.44,1.26)	0.93(0.65,1.32)	29/131	0.66(0.38,1.15)	0.73(0.39,1.37)	0.77(0.44,1.35)	0.87(0.57,1.32)
G:G	39/78	17/38	0.91(0.46,1.80)	0.86(0.39,1.89)	0.94(0.65,1.36)	0.87(0.50,1.52)	22/40	1.65(0.87,3.14)	1.43(0.68,2.98)	1.19(0.84,1.70)	1.38(0.68,2.78)
Log-Add			0.88(0.62,1.24)	0.85(0.59,1.24)	0.88(0.61,1.26)	0.93(0.73,1.18)		1.17(0.84,1.64)	1.13(0.78,1.64)	1.11(0.78,1.59)	1.12(0.84,1.48)
Dominant			0.71(0.44,1.14)	0.71(0.42,1.21)	0.77(0.47,1.27)	0.85(0.58,1.25)		0.89(0.55,1.46)	0.93(0.53,1.62)	0.93(0.55,1.57)	1.00(0.64,1.56)
Recessive			1.16(0.62,2.16)	1.02(0.50,2.07)	1.02(0.54,1.93)	0.93(0.50,1.73)		**2.02(1.12,3.64)**	1.69(0.86,3.31)	1.51(0.82,2.77)	1.30(0.80,2.10)
rs3929											
G:G	131/343	79/161	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	52/182	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:G	54/177	19/80	**0.48(0.27,0.85)**	**0.45(0.24,0.85)**	**0.54(0.31,0.95)**	0.80(0.55,1.17)	35/97	1.26(0.77,2.07)	1.44(0.82,2.56)	1.37(0.81,2.32)	1.08(0.67,1.75)
C:C	4/22	2/11	0.37(0.08,1.71)	0.33(0.06,1.69)	0.68(0.35,1.33)	0.75(0.45,1.24)	2/11	0.64(0.14,2.96)	0.52(0.10,2.83)	0.78(0.39,1.57)	0.91(0.38,2.20)
Log-Add			**0.52(0.32,0.84)**	**0.50(0.30,0.84)**	**0.56(0.34,0.90)**	0.85(0.67,1.08)		1.09(0.72,1.66)	1.17(0.72,1.89)	1.12(0.71,1.76)	1.02(0.69,1.51)
Dominant			**0.47(0.27,0.81)**	**0.44(0.25,0.80)**	**0.52(0.30,0.89)**	0.88(0.66,1.18)		1.20(0.74,1.95)	1.35(0.78,2.36)	1.27(0.76,2.13)	1.00(0.67,1.50)
Recessive			0.45(0.10,2.05)	0.42(0.08,2.08)	0.68(0.25,1.83)	0.68(0.13,3.56)		0.58(0.13,2.68)	0.49(0.09,2.62)	0.71(0.26,1.96)	0.76(0.20,2.83)
rs2292305											
T:T	76/247	36/109	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	40/138	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	91/212	50/106	1.43(0.86,2.37)	1.41(0.80,2.47)	1.33(0.79,2.23)	0.99(0.64,1.54)	41/106	1.33(0.81,2.21)	1.34(0.76,2.39)	1.27(0.75,2.15)	1.11(0.73,1.69)
C:C	20/66	14/31	1.37(0.66,2.85)	1.33(0.58,3.01)	1.12(0.76,1.65)	1.12(0.48,2.57)	6/35	0.59(0.23,1.51)	0.57(0.21,1.60)	0.78(0.49,1.25)	0.82(0.33,2.02)
Log-Add			1.23(0.88,1.72)	1.15(0.80,1.67)	1.19(0.83,1.71)	1.05(0.71,1.55)		0.95(0.67,1.36)	0.96(0.64,1.44)	0.94(0.64,1.39)	0.97(0.65,1.45)
Dominant			1.41(0.88,2.28)	1.29(0.77,2.16)	1.32(0.81,2.17)	1.03(0.64,1.68)		1.15(0.71,1.86)	1.15(0.67,1.97)	1.11(0.67,1.83)	0.99(0.70,1.40)
Recessive			1.13(0.57,2.23)	1.06(0.50,2.23)	1.08(0.55,2.10)	1.08(0.52,2.27)		0.52(0.21,1.27)	0.54(0.21,1.44)	0.64(0.29,1.38)	0.92(0.50,1.72)
rs2273368											
C:C	64/165	29/78	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	35/87	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)

C:T	78/247	46/111	1.11(0.64,1.93)	1.42(0.77,2.61)	1.33(0.77,2.31)	1.14(0.62,2.08)	32/136	0.58(0.34,1.01)	0.60(0.32,1.12)	0.65(0.37,1.14)	0.85(0.58,1.25)
T:T	42/116	23/58	1.07(0.56,2.03)	1.27(0.62,2.60)	1.10(0.78,1.54)	1.13(0.49,2.61)	19/58	0.81(0.43,1.56)	0.95(0.46,1.98)	0.99(0.70,1.41)	1.05(0.55,2.01)
Log-Add			1.04(0.75,1.43)	1.11(0.79,1.56)	1.13(0.80,1.58)	1.07(0.69,1.65)		0.85(0.61,1.19)	0.92(0.63,1.33)	0.92(0.64,1.32)	1.01(0.74,1.37)
Dominant			1.10(0.66,1.83)	1.38(0.79,2.41)	1.30(0.77,2.19)	0.94(0.70,1.28)		0.65(0.40,1.08)	0.71(0.40,1.24)	0.73(0.44,1.24)	0.93(0.63,1.37)
Recessive			1.00(0.58,1.74)	0.94(0.51,1.71)	1.02(0.58,1.79)	1.04(0.60,1.79)		1.09(0.61,1.96)	1.23(0.63,2.39)	1.18(0.65,2.16)	1.09(0.75,1.59)
rs2953											
T:T	100/310	53/135	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	47/175	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
G:T	66/192	40/103	0.99(0.61,1.61)	0.93(0.54,1.60)	0.94(0.57,1.54)	1.01(0.69,1.46)	26/89	1.09(0.63,1.87)	0.86(0.46,1.58)	0.87(0.50,1.53)	0.95(0.55,1.62)
G:G	22/38	9/16	1.43(0.60,3.44)	1.66(0.62,4.45)	1.25(0.79,1.99)	1.12(0.64,1.97)	13/22	**2.20(1.03,4.69)**	2.04(0.85,4.89)	1.39(0.92,2.11)	1.30(0.62,2.75)
Log-Add			1.10(0.76,1.58)	1.12(0.75,1.68)	1.10(0.74,1.64)	1.04(0.80,1.36)		1.36(0.96,1.93)	1.18(0.80,1.76)	1.21(0.82,1.78)	1.10(0.81,1.50)
Dominant			1.05(0.66,1.66)	1.01(0.61,1.67)	1.02(0.63,1.65)	0.96(0.73,1.26)		1.31(0.80,2.13)	1.04(0.60,1.80)	1.06(0.64,1.77)	1.03(0.76,1.39)
Recessive			1.44(0.61,3.37)	1.84(0.72,4.73)	1.44(0.65,3.18)	1.32(0.63,2.78)		**2.14(1.03,4.45)**	1.96(0.86,4.48)	1.75(0.85,3.63)	1.31(0.73,2.38)
Stem Cell Related											
rs6815391											
T:T	83/227	44/105	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	39/122	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	71/214	41/96	1.02(0.61,1.69)	1.09(0.62,1.91)	1.09(0.65,1.83)	0.96(0.71,1.29)	30/118	0.80(0.46,1.36)	0.86(0.46,1.57)	0.87(0.50,1.52)	0.89(0.59,1.35)
C:C	27/79	13/42	0.74(0.36,1.51)	0.68(0.31,1.49)	0.83(0.57,1.20)	0.94(0.57,1.56)	14/37	1.18(0.58,2.41)	1.32(0.59,2.94)	1.14(0.78,1.67)	0.94(0.50,1.77)
Log-Add			0.90(0.65,1.24)	0.91(0.64,1.29)	0.88(0.62,1.24)	0.97(0.77,1.22)		1.01(0.71,1.43)	1.07(0.73,1.58)	1.07(0.74,1.56)	0.96(0.72,1.29)
Dominant			0.93(0.58,1.50)	0.98(0.59,1.63)	0.96(0.59,1.55)	1.01(0.75,1.36)		0.89(0.54,1.45)	0.95(0.55,1.66)	0.97(0.58,1.63)	0.91(0.63,1.33)
Recessive			0.73(0.37,1.43)	0.70(0.34,1.45)	0.70(0.37,1.34)	0.92(0.63,1.33)		1.32(0.67,2.57)	1.42(0.67,3.02)	1.31(0.68,2.55)	1.05(0.61,1.81)
rs13409											
C:C	58/185	32/95	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	26/90	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	90/247	50/111	1.34(0.79,2.25)	1.20(0.68,2.12)	1.17(0.69,1.97)	1.04(0.64,1.71)	40/136	1.02(0.58,1.78)	1.00(0.53,1.87)	1.00(0.57,1.76)	0.90(0.60,1.34)
T:T	35/103	18/44	1.21(0.62,2.40)	1.05(0.49,2.25)	1.01(0.70,1.45)	1.02(0.55,1.91)	17/59	1.00(0.50,2.00)	0.99(0.45,2.15)	0.99(0.69,1.44)	0.95(0.58,1.56)
Log-Add			1.13(0.82,1.57)	1.06(0.75,1.52)	1.04(0.73,1.48)	1.01(0.74,1.39)		1.00(0.71,1.41)	0.99(0.67,1.45)	0.99(0.69,1.44)	0.97(0.76,1.24)
Dominant			1.30(0.80,2.13)	1.21(0.71,2.05)	1.13(0.69,1.87)	0.95(0.62,1.45)		1.01(0.60,1.71)	0.98(0.55,1.75)	1.00(0.58,1.71)	0.96(0.52,1.79)
Recessive			1.03(0.56,1.88)	0.92(0.47,1.79)	0.94(0.51,1.74)	0.92(0.62,1.38)		0.99(0.54,1.81)	0.99(0.50,1.97)	0.99(0.53,1.83)	0.95(0.52,1.73)
rs3130932											
T:T	87/252	49/111	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	38/141	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
G:T	76/215	37/106	0.79(0.48,1.31)	0.80(0.46,1.39)	0.82(0.49,1.38)	0.92(0.64,1.30)	39/109	1.33(0.80,2.22)	1.95(1.06,3.57)	**1.75(1.01,3.04)**	1.09(0.69,1.74)
G:G	22/68	14/31	1.02(0.50,2.09)	1.22(0.56,2.68)	1.11(0.76,1.61)	0.95(0.62,1.46)	8/37	0.80(0.35,1.87)	0.80(0.32,2.03)	0.89(0.57,1.37)	0.99(0.48,2.04)
Log-Add			0.94(0.67,1.32)	0.97(0.68,1.39)	1.01(0.71,1.45)	0.96(0.76,1.20)		1.02(0.72,1.45)	1.14(0.78,1.68)	1.11(0.77,1.61)	1.03(0.73,1.45)
Dominant			0.84(0.53,1.34)	0.86(0.52,1.43)	0.90(0.56,1.46)	0.90(0.56,1.45)		1.19(0.73,1.94)	1.54(0.88,2.68)	1.46(0.87,2.45)	1.13(0.77,1.66)
Recessive			1.14(0.58,2.25)	1.20(0.58,2.48)	1.27(0.65,2.45)	1.03(0.66,1.60)		0.70(0.31,1.57)	0.68(0.28,1.63)	0.70(0.34,1.46)	0.98(0.54,1.77)
rs2228224											
G:G	102/294	56/136	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	46/158	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	66/189	38/88	1.05(0.64,1.71)	1.20(0.69,2.09)	1.18(0.70,1.96)	0.88(0.63,1.22)	28/101	0.95(0.56,1.62)	1.08(0.59,1.97)	1.06(0.61,1.84)	1.06(0.61,1.83)
A:A	11/44	5/24	0.51(0.18,1.39)	0.52(0.18,1.50)	0.74(0.46,1.20)	0.67(0.33,1.36)	6/20	1.03(0.39,2.72)	1.43(0.47,4.32)	1.17(0.70,1.95)	0.96(0.47,1.98)
Log-Add			0.86(0.59,1.24)	0.90(0.61,1.34)	0.90(0.61,1.31)	0.86(0.69,1.07)		0.99(0.66,1.47)	1.14(0.73,1.78)	1.13(0.74,1.73)	1.03(0.75,1.41)
Dominant			0.93(0.58,1.49)	1.03(0.62,1.73)	1.02(0.62,1.66)	0.99(0.72,1.35)		0.97(0.58,1.60)	1.16(0.66,2.03)	1.11(0.66,1.88)	1.10(0.75,1.60)

Recessive			0.50(0.18,1.34)	0.49(0.17,1.38)	0.61(0.28,1.35)	0.91(0.48,1.71)		1.05(0.41,2.71)	1.28(0.44,3.70)	1.23(0.52,2.91)	1.10(0.40,2.99)
rs1126497											
C:C	106/362	56/179	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	50/183	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	73/156	40/71	**1.80(1.10,2.94)**	**2.28(1.28,4.04)**	**2.04(1.21,3.44)**	1.17(0.84,1.64)	33/85	1.42(0.85,2.36)	**2.23(1.21,4.10)**	**1.96(1.13,3.42)**	1.20(0.69,2.11)
T:T	7/28	3/8	1.20(0.31,4.67)	2.10(0.49,8.96)	1.30(0.68,2.50)	1.11(0.44,2.79)	4/20	0.73(0.24,2.24)	0.61(0.18,2.10)	0.80(0.46,1.39)	0.85(0.29,2.45)
Log-Add			**1.51(1.00,2.28)**	**2.03(1.27,3.24)**	**1.80(1.15,2.83)**	1.13(0.86,1.47)		1.10(0.75,1.62)	1.27(0.83,1.93)	1.22(0.81,1.83)	1.08(0.75,1.57)
Dominant			**1.74(1.08,2.80)**	**2.49(1.43,4.31)**	**2.05(1.22,3.43)**	1.20(0.88,1.64)		1.29(0.79,2.10)	**1.81(1.03,3.18)**	1.61(0.96,2.72)	1.11(0.66,1.85)
Recessive			0.98(0.25,3.76)	1.34(0.33,5.53)	1.18(0.43,3.25)	1.36(0.39,4.79)		0.65(0.21,1.94)	0.48(0.14,1.60)	0.66(0.27,1.58)	0.76(0.26,2.26)
rs3740535											
G:G	95/293	53/130	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	42/163	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	68/211	33/108	0.75(0.45,1.24)	0.62(0.35,1.08)	0.66(0.39,1.11)	0.88(0.63,1.22)	35/103	1.32(0.79,2.20)	0.95(0.53,1.71)	0.95(0.56,1.63)	1.00(0.71,1.43)
A:A	23/35	14/14	**2.45(1.09,5.49)**	2.31(0.93,5.74)	1.47(0.95,2.26)	1.02(0.63,1.65)	9/21	1.66(0.71,3.90)	1.44(0.56,3.72)	1.18(0.75,1.85)	1.14(0.51,2.56)
Log-Add			1.19(0.83,1.70)	1.09(0.74,1.61)	1.07(0.72,1.57)	0.97(0.78,1.22)		1.30(0.90,1.88)	1.08(0.71,1.65)	1.09(0.73,1.63)	1.04(0.77,1.39)
Dominant			0.94(0.59,1.50)	0.86(0.52,1.43)	0.82(0.51,1.34)	0.92(0.63,1.34)		1.38(0.85,2.23)	1.02(0.59,1.76)	1.03(0.62,1.71)	1.04(0.73,1.46)
Recessive			**2.77(1.27,6.04)**	**2.43(1.03,5.73)**	2.06(0.97,4.35)	1.30(0.63,2.69)		1.48(0.65,3.37)	1.44(0.57,3.63)	1.31(0.60,2.83)	1.03(0.50,2.12)
rs915894											
C:C	51/152	32/66	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	19/86	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:C	90/271	47/131	0.74(0.43,1.27)	0.80(0.44,1.45)	0.83(0.48,1.44)	0.89(0.59,1.33)	43/140	1.39(0.76,2.54)	1.15(0.58,2.28)	1.09(0.59,2.01)	1.01(0.69,1.49)
A:A	37/107	18/55	0.67(0.34,1.33)	0.79(0.38,1.65)	0.90(0.64,1.28)	0.82(0.51,1.32)	19/52	1.65(0.80,3.41)	1.95(0.87,4.36)	1.35(0.93,1.96)	1.33(0.71,2.49)
Log-Add			0.81(0.58,1.14)	0.86(0.60,1.23)	0.89(0.62,1.27)	0.92(0.72,1.16)		1.29(0.90,1.84)	1.38(0.92,2.09)	1.35(0.91,2.00)	1.13(0.83,1.53)
Dominant			0.72(0.43,1.20)	0.80(0.46,1.39)	0.82(0.49,1.39)	0.92(0.65,1.31)		1.46(0.82,2.59)	1.32(0.70,2.52)	1.28(0.71,2.28)	1.01(0.71,1.43)
Recessive			0.82(0.45,1.48)	0.83(0.44,1.57)	0.92(0.52,1.65)	0.92(0.67,1.28)		1.33(0.73,2.42)	1.79(0.92,3.51)	1.60(0.87,2.92)	1.12(0.57,2.20)
rs1046472											
C:C	123/350	63/173	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	60/177	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:C	60/167	36/72	1.37(0.84,2.25)	1.31(0.76,2.27)	1.27(0.76,2.11)	1.07(0.80,1.43)	24/95	0.75(0.44,1.27)	0.66(0.36,1.22)	0.71(0.41,1.23)	0.91(0.58,1.44)
A:A	6/19	2/8	0.69(0.14,3.32)	0.77(0.14,4.10)	0.89(0.44,1.81)	0.87(0.34,2.27)	4/11	1.07(0.33,3.50)	0.85(0.23,3.13)	0.94(0.52,1.69)	0.94(0.48,1.85)
Log-Add			1.18(0.77,1.80)	1.14(0.72,1.81)	1.14(0.73,1.77)	1.01(0.78,1.31)		0.85(0.55,1.32)	0.78(0.48,1.26)	0.79(0.50,1.24)	0.96(0.71,1.29)
Dominant			1.30(0.81,2.11)	1.25(0.74,2.11)	1.22(0.74,2.01)	1.02(0.73,1.41)		0.78(0.47,1.30)	0.69(0.39,1.22)	0.73(0.43,1.23)	0.88(0.61,1.28)
Recessive			0.62(0.13,2.97)	0.62(0.12,3.27)	0.85(0.30,2.41)	0.57(0.11,3.07)		1.18(0.37,3.79)	1.05(0.29,3.81)	0.98(0.38,2.53)	1.02(0.32,3.27)
rs3734637											
A:A	114/310	64/140	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	50/170	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:C	60/191	33/96	0.75(0.46,1.23)	0.66(0.38,1.16)	0.71(0.43,1.19)	0.80(0.57,1.14)	27/95	0.97(0.57,1.64)	0.60(0.32,1.11)	0.65(0.37,1.14)	0.85(0.54,1.34)
C:C	8/35	2/17	0.26(0.06,1.15)	0.20(0.04,1.02)	0.54(0.28,1.03)	0.79(0.47,1.33)	6/18	1.13(0.43,3.01)	0.83(0.29,2.41)	0.93(0.57,1.53)	1.17(0.41,3.31)
Log-Add			0.66(0.44,1.00)	**0.62(0.39,0.97)**	**0.61(0.39,0.95)**	0.86(0.69,1.08)		1.02(0.69,1.51)	0.74(0.47,1.17)	0.78(0.50,1.20)	0.94(0.62,1.42)
Dominant			0.68(0.42,1.10)	0.64(0.38,1.08)	0.63(0.38,1.04)	0.88(0.66,1.17)		0.99(0.60,1.64)	0.62(0.35,1.11)	0.68(0.40,1.16)	0.86(0.55,1.35)
Recessive			0.29(0.06,1.26)	0.24(0.05,1.15)	0.49(0.19,1.28)	0.98(0.31,3.02)		1.15(0.44,2.99)	0.97(0.34,2.72)	1.00(0.44,2.30)	0.97(0.35,2.67)
rs520692											
A:A	141/396	75/181	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	66/215	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	42/124	21/66	0.77(0.44,1.34)	0.76(0.41,1.42)	0.82(0.47,1.43)	0.90(0.59,1.37)	21/58	1.18(0.67,2.09)	0.96(0.50,1.84)	0.97(0.54,1.74)	0.81(0.45,1.45)
G:G	4/17	3/6	1.21(0.29,4.95)	1.28(0.27,6.13)	1.08(0.55,2.14)	0.90(0.49,1.63)	1/11	0.30(0.04,2.34)	0.50(0.06,4.09)	0.80(0.36,1.76)	0.50(0.05,5.03)
Log-Add			0.87(0.55,1.39)	0.89(0.54,1.47)	0.90(0.56,1.45)	0.94(0.72,1.23)		0.92(0.58,1.48)	0.89(0.52,1.55)	0.89(0.53,1.48)	0.80(0.46,1.39)

Dominant			0.80(0.47,1.37)	0.82(0.46,1.45)	0.85(0.50,1.46)	0.95(0.72,1.27)		1.04(0.60,1.81)	0.93(0.50,1.74)	0.92(0.52,1.63)	0.92(0.58,1.46)
Recessive			1.29(0.32,5.25)	1.46(0.32,6.70)	1.12(0.39,3.17)	1.25(0.29,5.36)		0.29(0.04,2.24)	0.50(0.06,4.20)	0.79(0.26,2.37)	0.59(0.09,4.04)
rs8708											
A:A	123/360	65/159	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	58/201	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	53/147	30/73	1.01(0.60,1.68)	1.03(0.58,1.82)	1.03(0.61,1.74)	0.94(0.64,1.38)	23/74	1.08(0.62,1.87)	1.08(0.58,2.02)	1.06(0.60,1.88)	1.06(0.68,1.66)
G:G	9/23	6/15	0.98(0.36,2.63)	1.47(0.50,4.31)	1.19(0.72,1.96)	0.93(0.39,2.21)	3/8	1.30(0.33,5.06)	1.52(0.31,7.45)	1.17(0.58,2.35)	1.08(0.26,4.50)
Log-Add			1.00(0.68,1.46)	1.10(0.72,1.67)	1.12(0.74,1.68)	0.94(0.70,1.27)		1.10(0.70,1.73)	1.10(0.66,1.83)	1.12(0.69,1.81)	1.06(0.73,1.53)
Dominant			1.00(0.62,1.62)	1.07(0.63,1.81)	1.09(0.66,1.79)	0.91(0.66,1.26)		1.10(0.65,1.87)	1.08(0.59,1.95)	1.10(0.63,1.90)	0.94(0.47,1.88)
Recessive			0.98(0.37,2.59)	1.40(0.49,3.95)	1.27(0.54,2.97)	1.00(0.44,2.27)		1.27(0.33,4.91)	1.45(0.31,6.81)	1.19(0.41,3.41)	1.20(0.33,4.40)
rs1421											
A:A	121/359	65/162	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	56/197	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	61/156	32/79	1.01(0.61,1.67)	0.75(0.42,1.34)	0.79(0.46,1.34)	0.98(0.73,1.31)	29/77	1.32(0.79,2.23)	1.73(0.93,3.20)	1.57(0.89,2.75)	1.16(0.74,1.80)
G:G	5/16	2/7	0.71(0.14,3.52)	0.96(0.18,5.07)	1.00(0.49,2.04)	1.04(0.46,2.38)	3/9	1.17(0.31,4.48)	1.72(0.40,7.35)	1.23(0.64,2.35)	1.39(0.56,3.48)
Log-Add			0.96(0.62,1.49)	0.87(0.53,1.41)	0.84(0.52,1.34)	0.99(0.75,1.30)		1.23(0.80,1.89)	1.56(0.96,2.54)	1.47(0.92,2.32)	1.19(0.84,1.70)
Dominant			0.99(0.60,1.61)	0.84(0.49,1.44)	0.80(0.48,1.34)	0.96(0.68,1.35)		1.31(0.79,2.16)	1.77(0.99,3.18)	1.59(0.92,2.73)	1.24(0.82,1.86)
Recessive			0.71(0.14,3.48)	0.99(0.19,5.25)	1.03(0.36,2.99)	1.38(0.50,3.79)		1.07(0.28,4.06)	1.42(0.34,6.03)	1.21(0.44,3.34)	1.76(0.44,6.97)
rs2269700											
T:T	121/362	68/174	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	53/188	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	57/163	30/71	1.08(0.65,1.80)	1.05(0.60,1.84)	1.06(0.63,1.78)	0.96(0.53,1.73)	27/92	1.04(0.62,1.76)	1.08(0.59,1.96)	1.06(0.61,1.83)	1.02(0.59,1.75)
C:C	6/15	3/10	0.77(0.21,2.87)	0.88(0.22,3.49)	0.94(0.51,1.74)	0.91(0.32,2.63)	3/5	2.13(0.49,9.20)	1.91(0.34,10.76	1.26(0.60,2.63)	1.90(0.46,7.81)
Log-Add			1.00(0.66,1.52)	0.99(0.63,1.56)	1.01(0.66,1.55)	0.97(0.64,1.47)		1.15(0.73,1.82)	1.14(0.67,1.93)	1.14(0.69,1.86)	1.11(0.70,1.77)
Dominant			1.04(0.64,1.71)	1.00(0.59,1.69)	1.03(0.63,1.70)	1.00(0.75,1.35)		1.10(0.66,1.83)	1.10(0.61,1.98)	1.10(0.64,1.89)	1.08(0.68,1.74)
Recessive			0.75(0.20,2.78)	0.94(0.23,3.76)	0.92(0.35,2.41)	0.88(0.25,3.13)		2.10(0.49,8.98)	1.84(0.33,10.30	1.27(0.42,3.79)	1.96(0.42,9.08)
rs2240308											
G:G	86/252	41/117	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	45/135	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	76/203	44/96	1.31(0.79,2.16)	1.16(0.64,2.10)	1.11(0.65,1.90)	0.94(0.62,1.44)	32/107	0.90(0.53,1.51)	0.76(0.41,1.43)	0.80(0.45,1.42)	0.91(0.62,1.35)
A:A	23/46	14/21	1.90(0.89,4.09)	1.81(0.76,4.30)	1.29(0.86,1.94)	0.93(0.51,1.71)	9/25	1.08(0.47,2.48)	0.79(0.30,2.10)	0.91(0.58,1.43)	0.89(0.36,2.20)
Log-Add			1.36(0.96,1.92)	1.35(0.91,2.01)	1.25(0.85,1.84)	0.96(0.69,1.32)		0.98(0.68,1.42)	0.84(0.55,1.30)	0.86(0.57,1.30)	0.93(0.64,1.36)
Dominant			1.41(0.88,2.27)	1.35(0.78,2.34)	1.22(0.73,2.04)	0.99(0.58,1.69)		0.93(0.57,1.52)	0.77(0.43,1.38)	0.80(0.47,1.37)	0.89(0.55,1.45)
Recessive			1.67(0.81,3.44)	1.77(0.80,3.93)	1.45(0.72,2.93)	1.08(0.58,1.98)		1.13(0.51,2.53)	0.87(0.34,2.22)	0.92(0.43,2.00)	0.94(0.40,2.24)
rs3729629											
G:G	92/236	48/116	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	44/120	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:G	75/233	37/106	0.84(0.51,1.40)	0.66(0.37,1.17)	0.71(0.42,1.19)	0.85(0.61,1.18)	38/127	0.82(0.49,1.35)	0.73(0.41,1.29)	0.77(0.46,1.31)	0.84(0.53,1.33)
C:C	20/66	14/31	1.09(0.53,2.23)	0.90(0.41,1.99)	0.98(0.67,1.43)	0.82(0.44,1.52)	6/35	0.47(0.18,1.19)	0.57(0.20,1.62)	0.79(0.49,1.28)	0.66(0.34,1.26)
Log-Add			0.98(0.70,1.38)	0.88(0.61,1.28)	0.88(0.62,1.27)	0.88(0.66,1.18)		0.74(0.51,1.07)	0.77(0.50,1.18)	0.77(0.51,1.16)	0.81(0.60,1.10)
Dominant			0.90(0.56,1.43)	0.72(0.43,1.20)	0.76(0.46,1.23)	0.96(0.65,1.40)		0.74(0.46,1.20)	0.72(0.41,1.24)	0.74(0.44,1.23)	0.97(0.62,1.51)
Recessive			1.18(0.60,2.33)	1.21(0.58,2.52)	1.10(0.57,2.11)	0.91(0.50,1.65)		0.52(0.21,1.27)	0.73(0.27,1.95)	0.77(0.35,1.71)	0.86(0.51,1.46)
rs4730775											
C:C	96/307	51/141	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	45/166	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	74/182	36/89	1.12(0.68,1.85)	0.87(0.49,1.52)	0.89(0.53,1.49)	0.91(0.58,1.43)	38/93	1.51(0.91,2.49)	1.45(0.82,2.55)	1.38(0.82,2.32)	1.12(0.76,1.65)
T:T	16/42	13/17	2.11(0.96,4.66)	2.33(0.97,5.56)	1.46(0.96,2.21)	1.19(0.64,2.22)	3/25	0.44(0.13,1.53)	0.49(0.13,1.84)	0.74(0.41,1.32)	0.94(0.50,1.78)

Log-Add			1.33(0.93,1.88)	1.22(0.83,1.78)	1.23(0.85,1.78)	1.03(0.74,1.43)		1.02(0.70,1.49)	1.03(0.67,1.59)	1.02(0.67,1.54)	1.02(0.77,1.35)
Dominant			1.28(0.80,2.04)	1.08(0.65,1.79)	1.07(0.66,1.74)	1.00(0.73,1.39)		1.28(0.79,2.08)	1.26(0.73,2.16)	1.21(0.73,2.01)	0.97(0.53,1.77)
Recessive			2.02(0.94,4.34)	2.12(0.92,4.89)	1.88(0.91,3.90)	1.23(0.75,2.02)		0.37(0.11,1.27)	0.45(0.12,1.64)	0.62(0.25,1.52)	0.74(0.33,1.64)
rs4835761											
A:A	65/175	32/91	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	33/84	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	82/237	47/111	1.20(0.71,2.04)	1.26(0.70,2.25)	1.20(0.71,2.05)	0.96(0.67,1.38)	35/126	0.71(0.41,1.23)	0.63(0.33,1.18)	0.68(0.38,1.21)	0.76(0.48,1.18)
G:G	38/98	19/37	1.46(0.74,2.89)	1.62(0.75,3.50)	1.23(0.86,1.78)	1.04(0.54,2.02)	19/61	0.79(0.41,1.52)	0.80(0.38,1.69)	0.92(0.64,1.31)	1.00(0.50,1.96)
Log-Add			1.21(0.86,1.69)	1.16(0.81,1.67)	1.24(0.87,1.79)	1.01(0.73,1.42)		0.87(0.62,1.21)	0.88(0.60,1.28)	0.87(0.60,1.25)	0.97(0.68,1.37)
Dominant			1.27(0.77,2.08)	1.18(0.69,2.02)	1.28(0.77,2.14)	0.96(0.72,1.28)		0.74(0.44,1.22)	0.67(0.38,1.19)	0.72(0.42,1.23)	0.81(0.57,1.17)
Recessive			1.31(0.71,2.42)	1.27(0.65,2.50)	1.31(0.71,2.44)	1.07(0.76,1.51)		0.96(0.54,1.72)	1.13(0.59,2.18)	1.03(0.56,1.87)	0.92(0.43,2.00)
rs2241802											
G:G	66/159	33/79	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	33/80	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	89/243	51/116	1.05(0.62,1.78)	1.32(0.73,2.38)	1.25(0.73,2.13)	1.07(0.63,1.83)	38/127	0.73(0.42,1.25)	0.70(0.37,1.30)	0.74(0.42,1.31)	0.82(0.53,1.26)
A:A	33/115	17/47	0.87(0.44,1.72)	0.97(0.44,2.12)	0.97(0.67,1.40)	1.00(0.63,1.57)	16/68	0.57(0.29,1.12)	0.77(0.35,1.67)	0.90(0.62,1.30)	0.69(0.39,1.23)
Log-Add			0.95(0.68,1.32)	1.00(0.70,1.44)	1.02(0.72,1.46)	1.00(0.79,1.26)		0.75(0.54,1.05)	0.83(0.56,1.22)	0.86(0.59,1.25)	0.83(0.62,1.10)
Dominant			1.00(0.61,1.64)	1.12(0.65,1.91)	1.17(0.70,1.95)	1.08(0.80,1.46)		0.67(0.41,1.11)	0.69(0.39,1.23)	0.75(0.44,1.29)	0.83(0.58,1.20)
Recessive			0.84(0.46,1.55)	0.85(0.43,1.68)	0.86(0.46,1.60)	0.93(0.56,1.54)		0.69(0.37,1.26)	0.93(0.47,1.85)	0.96(0.52,1.78)	0.86(0.58,1.28)
rs222851											
A:A	70/219	41/107	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	29/112	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	90/234	47/110	1.12(0.68,1.83)	1.22(0.70,2.12)	1.19(0.71,1.98)	0.89(0.61,1.32)	43/124	1.34(0.78,2.29)	1.26(0.68,2.34)	1.19(0.69,2.08)	1.01(0.68,1.50)
G:G	25/72	12/31	1.01(0.47,2.15)	0.91(0.39,2.11)	0.95(0.64,1.42)	0.90(0.36,2.26)	13/41	1.22(0.58,2.58)	1.70(0.72,4.03)	1.26(0.84,1.89)	1.15(0.61,2.19)
Log-Add			1.04(0.74,1.46)	1.02(0.70,1.49)	1.02(0.71,1.47)	0.93(0.62,1.40)		1.15(0.81,1.63)	1.27(0.84,1.92)	1.27(0.85,1.88)	1.06(0.78,1.44)
Dominant			1.09(0.68,1.75)	1.08(0.65,1.81)	1.13(0.69,1.84)	0.91(0.62,1.34)		1.31(0.79,2.18)	1.35(0.75,2.41)	1.28(0.75,2.19)	0.98(0.69,1.40)
Recessive			0.95(0.47,1.94)	0.93(0.43,1.99)	0.86(0.44,1.69)	0.83(0.52,1.33)		1.04(0.53,2.05)	1.39(0.64,3.03)	1.35(0.68,2.68)	0.98(0.50,1.95)
rs1981492											
G:G	103/274	58/127	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	45/147	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:G	65/206	34/92	0.81(0.49,1.34)	0.83(0.47,1.46)	0.85(0.51,1.43)	0.95(0.58,1.54)	31/114	0.89(0.53,1.49)	0.68(0.38,1.23)	0.72(0.42,1.24)	0.94(0.60,1.47)
A:A	14/46	7/26	0.59(0.24,1.44)	0.68(0.25,1.84)	0.84(0.53,1.34)	0.94(0.63,1.40)	7/20	1.14(0.45,2.88)	0.94(0.33,2.68)	0.98(0.60,1.60)	1.03(0.44,2.39)
Log-Add			0.78(0.55,1.13)	0.84(0.56,1.25)	0.83(0.56,1.23)	0.97(0.79,1.19)		0.99(0.67,1.45)	0.83(0.53,1.30)	0.84(0.55,1.28)	0.99(0.74,1.31)
Dominant			0.76(0.47,1.22)	0.82(0.49,1.38)	0.82(0.50,1.34)	0.98(0.77,1.24)		0.93(0.57,1.51)	0.72(0.41,1.26)	0.75(0.45,1.26)	0.95(0.59,1.55)
Recessive			0.64(0.27,1.53)	0.72(0.28,1.86)	0.80(0.36,1.76)	1.07(0.63,1.84)		1.20(0.49,2.95)	1.13(0.41,3.09)	1.07(0.47,2.43)	1.12(0.44,2.85)
rs6754757											
T:T	113/311	59/136	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	54/175	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
G:T	65/153	36/78	1.06(0.65,1.75)	1.00(0.56,1.79)	1.01(0.59,1.71)	0.94(0.62,1.43)	29/75	1.25(0.74,2.12)	1.03(0.54,1.94)	1.03(0.58,1.84)	1.01(0.62,1.62)
G:G	9/38	5/17	0.68(0.24,1.92)	0.93(0.29,3.00)	0.96(0.56,1.64)	0.94(0.47,1.89)	4/21	0.62(0.20,1.88)	0.48(0.13,1.79)	0.74(0.42,1.33)	0.81(0.36,1.82)
Log-Add			0.94(0.64,1.37)	0.93(0.60,1.44)	0.98(0.64,1.50)	0.96(0.70,1.32)		0.98(0.67,1.45)	0.82(0.51,1.31)	0.86(0.55,1.35)	0.95(0.73,1.25)
Dominant			0.99(0.62,1.60)	0.96(0.56,1.65)	0.99(0.59,1.66)	1.05(0.69,1.60)		1.11(0.68,1.84)	0.88(0.48,1.60)	0.92(0.53,1.60)	0.89(0.57,1.39)
Recessive			0.66(0.24,1.85)	0.74(0.24,2.30)	0.95(0.39,2.28)	0.99(0.45,2.19)		0.57(0.19,1.72)	0.45(0.12,1.60)	0.67(0.27,1.67)	0.67(0.29,1.58)
HIF-1α pathway											
rs2295778											

C:C	104/304	60/130	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	44/174	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:G	65/169	31/90	0.75(0.45,1.24)	0.75(0.41,1.37)	0.79(0.46,1.36)	0.86(0.56,1.33)	34/79	**1.70(1.01,2.86)**	1.50(0.81,2.76)	1.39(0.80,2.43)	1.02(0.64,1.64)
G:G	14/29	7/15	1.01(0.39,2.61)	1.22(0.43,3.47)	1.10(0.67,1.80)	0.89(0.46,1.72)	7/14	1.98(0.75,5.19)	1.40(0.43,4.54)	1.14(0.66,1.96)	1.13(0.50,2.58)
Log-Add			0.87(0.59,1.29)	0.86(0.56,1.32)	0.94(0.62,1.43)	0.90(0.63,1.27)		**1.53(1.04,2.25)**	1.31(0.83,2.07)	1.28(0.83,1.99)	1.06(0.75,1.49)
Dominant			0.78(0.48,1.27)	0.75(0.44,1.30)	0.85(0.51,1.42)	0.90(0.59,1.37)		**1.74(1.06,2.86)**	1.46(0.82,2.61)	1.39(0.82,2.38)	1.09(0.74,1.61)
Recessive			1.13(0.45,2.86)	1.16(0.42,3.20)	1.21(0.53,2.79)	1.11(0.49,2.53)		1.62(0.63,4.16)	1.22(0.39,3.82)	1.12(0.46,2.72)	1.02(0.50,2.06)
rs2057482											
C:C	124/340	72/153	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	52/187	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
T:C	58/157	25/80	0.66(0.39,1.13)	0.71(0.39,1.28)	0.74(0.43,1.27)	0.85(0.63,1.14)	33/77	1.54(0.93,2.57)	1.57(0.88,2.80)	1.47(0.86,2.51)	1.17(0.62,2.21)
T:T	8/28	4/13	0.65(0.21,2.08)	0.81(0.23,2.84)	0.91(0.52,1.61)	0.95(0.44,2.09)	4/15	0.96(0.31,3.01)	0.67(0.17,2.63)	0.84(0.46,1.55)	1.19(0.43,3.27)
Log-Add			0.72(0.47,1.10)	0.74(0.46,1.17)	0.80(0.51,1.24)	0.90(0.69,1.17)		1.24(0.84,1.84)	1.15(0.73,1.81)	1.16(0.75,1.78)	1.16(0.78,1.70)
Dominant			0.66(0.40,1.10)	0.66(0.38,1.14)	0.74(0.44,1.25)	0.88(0.54,1.42)		1.45(0.89,2.36)	1.39(0.80,2.42)	1.34(0.80,2.25)	1.22(0.73,2.03)
Recessive			0.74(0.24,2.32)	0.93(0.27,3.13)	0.94(0.37,2.34)	0.97(0.24,3.91)		0.83(0.27,2.56)	0.52(0.13,2.03)	0.75(0.29,1.94)	0.86(0.29,2.59)
NFKB Pathway											
rs2230793											
A:A	101/240	57/107	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	44/133	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
A:C	68/238	37/121	**0.57(0.35,0.94)**	**0.50(0.29,0.87)**	**0.57(0.34,0.94)**	0.80(0.54,1.19)	31/117	0.80(0.47,1.35)	0.76(0.42,1.37)	0.79(0.46,1.35)	0.91(0.62,1.33)
C:C	18/53	7/22	0.60(0.24,1.48)	0.64(0.24,1.74)	0.83(0.52,1.31)	0.73(0.35,1.48)	11/31	1.07(0.50,2.31)	1.01(0.43,2.37)	1.01(0.67,1.52)	0.93(0.55,1.56)
Log-Add			**0.67(0.46,0.98)**	0.67(0.44,1.01)	**0.67(0.45,1.00)**	0.84(0.61,1.17)		0.96(0.67,1.37)	0.92(0.62,1.37)	0.93(0.63,1.36)	0.95(0.74,1.22)
Dominant			**0.58(0.36,0.92)**	**0.55(0.33,0.91)**	**0.58(0.35,0.93)**	0.91(0.68,1.22)		0.86(0.53,1.39)	0.83(0.48,1.42)	0.84(0.50,1.38)	0.99(0.69,1.42)
Recessive			0.77(0.32,1.87)	0.93(0.36,2.39)	0.89(0.41,1.95)	1.01(0.58,1.78)		1.18(0.57,2.47)	1.11(0.49,2.52)	1.10(0.54,2.23)	1.09(0.65,1.83)
rs1538660											
C:C	85/235	49/104	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	36/131	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	81/238	40/114	0.74(0.45,1.22)	0.67(0.38,1.16)	0.70(0.42,1.17)	0.89(0.56,1.42)	41/124	1.20(0.72,2.00)	1.15(0.64,2.05)	1.12(0.66,1.90)	1.09(0.68,1.74)
T:T	21/55	11/28	0.83(0.38,1.81)	0.72(0.30,1.69)	0.86(0.58,1.30)	0.80(0.34,1.92)	10/27	1.35(0.60,3.04)	1.55(0.61,3.94)	1.21(0.78,1.88)	1.21(0.54,2.73)
Log-Add			0.85(0.60,1.21)	0.78(0.53,1.15)	0.79(0.54,1.15)	0.90(0.58,1.39)		1.17(0.82,1.69)	1.20(0.79,1.82)	1.19(0.80,1.78)	1.10(0.75,1.62)
Dominant			0.76(0.48,1.22)	0.68(0.41,1.13)	0.71(0.44,1.14)	0.82(0.52,1.29)		1.23(0.76,2.00)	1.19(0.69,2.06)	1.18(0.71,1.97)	1.07(0.74,1.56)
Recessive			0.96(0.46,2.02)	0.87(0.38,1.96)	0.89(0.44,1.79)	0.93(0.49,1.78)		1.23(0.57,2.65)	1.44(0.60,3.46)	1.30(0.62,2.75)	1.23(0.64,2.35)
rs12894467											
T:T	100/338	54/157	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	46/181	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	76/158	42/75	**1.63(1.00,2.65)**	**2.27(1.29,3.99)**	**2.03(1.21,3.40)**	1.09(0.67,1.75)	34/83	1.61(0.96,2.69)	1.29(0.72,2.31)	1.24(0.73,2.13)	1.04(0.67,1.61)
C:C	7/26	4/12	0.97(0.30,3.13)	1.66(0.46,5.97)	1.20(0.67,2.15)	0.99(0.45,2.17)	3/14	0.84(0.23,3.06)	0.94(0.22,3.97)	0.97(0.51,1.83)	0.96(0.40,2.27)
Log-Add			1.31(0.89,1.94)	**1.60(1.04,2.47)**	**1.66(1.09,2.53)**	1.03(0.72,1.47)		1.27(0.84,1.91)	1.19(0.74,1.91)	1.13(0.72,1.78)	1.01(0.70,1.46)
Dominant			1.54(0.96,2.47)	**1.93(1.14,3.28)**	**1.98(1.20,3.28)**	1.14(0.70,1.85)		1.50(0.91,2.47)	1.31(0.75,2.29)	1.21(0.72,2.05)	1.10(0.70,1.74)
Recessive			0.81(0.25,2.56)	1.08(0.31,3.81)	1.10(0.43,2.78)	1.40(0.48,4.06)		0.71(0.20,2.52)	0.87(0.21,3.61)	0.92(0.34,2.47)	1.15(0.42,3.15)
rs8904											
C:C	72/205	37/98	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	35/107	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)
C:T	80/233	46/112	1.09(0.65,1.81)	1.09(0.61,1.94)	1.05(0.62,1.78)	0.99(0.68,1.44)	34/121	0.86(0.50,1.47)	0.84(0.45,1.55)	0.86(0.49,1.51)	0.98(0.62,1.55)
T:T	35/95	18/41	1.16(0.59,2.27)	1.16(0.56,2.40)	1.07(0.76,1.51)	0.93(0.57,1.53)	17/54	0.96(0.49,1.87)	1.14(0.54,2.41)	1.07(0.75,1.53)	1.02(0.49,2.14)
Log-Add			1.08(0.78,1.49)	1.12(0.79,1.60)	1.07(0.76,1.51)	0.97(0.76,1.25)		0.96(0.69,1.34)	1.04(0.72,1.51)	1.03(0.72,1.48)	1.00(0.72,1.39)

Dominant	1.11(0.69,1.79)	1.18(0.70,1.99)	1.08(0.65,1.78)	1.09(0.71,1.66)	0.89(0.54,1.46)	0.94(0.54,1.64)	0.94(0.56,1.58)	1.00(0.69,1.43)
Recessive	1.11(0.60,2.04)	1.16(0.60,2.26)	1.10(0.61,1.99)	1.06(0.71,1.58)	1.04(0.57,1.91)	1.27(0.65,2.49)	1.20(0.65,2.20)	1.14(0.56,2.34)

Notation: Age (continuous variable), BMI categories, tobacco smoking status, pack-years of smoking, and county of residence were the covariates adjusted for in all multivariable logistic regression models.

Table 3-9. Menstrual and reproductive factors in association with the risk of lung cancer in the genotyped population

	All				
	Cases, n=191		Ctrls, n=564		Adjusted OR[1]
	N	%	N	%	(95% CI)
Menstrual Characteristics					
Age at menarche					
<=15	54	28.57	139	24.82	1.00(ref)
16-17	76	40.21	253	45.18	0.77(0.49 , 1.22)
>=18	59	31.22	168	30.00	0.88(0.54 , 1.43)
P_{trend}[4]					0.643
As a continuous variable[8]					1.01(0.91 , 1.11)
Age at menopause[5]					
<46	30	16.30	84	15.25	1.00(ref)
46-54	129	70.11	424	76.95	0.68(0.41 , 1.14)
>54	25	13.59	43	7.80	1.18(0.57 , 2.43)
P_{trend}					0.925
As a continuous variable[8]					1.01(0.96 , 1.05)
Reproductive window					
<=32	81	43.55	259	47.01	1.00(ref)
33-35	54	29.03	154	27.95	0.98(0.63 , 1.52)
>=36	51	27.42	138	25.05	1.03(0.65 , 1.62)
P_{trend}					0.925
As a continuous variable[8]					0.99(0.95 , 1.03)
Reproductive History					
Parity[6]					
0 or 1	26	13.61	60	10.64	1.00(ref)
2-3	76	39.79	205	36.35	0.88(0.48 , 1.62)
4 or more	89	46.60	299	53.01	0.84(0.46 , 1.54)
P_{trend}					0.603
As a continuous variable[8]					1.03(0.92 , 1.14)
Gravidity[6]					
0 or 1	21	10.99	48	8.51	1.00(ref)
2-3	56	29.32	168	29.79	0.76(0.38 , 1.53)
4 or more	114	59.69	348	61.70	0.98(0.51 , 1.88)
P_{trend}					0.589
As continuous variable[8]					1.04(0.95 , 1.14)
Number of live birth[6]					
0 or 1	26	13.61	66	11.70	1.00(ref)
2-3	77	40.31	208	36.88	0.95(0.52 , 1.75)
4 or more	88	46.07	290	51.42	0.92(0.51 , 1.68)
P_{trend}					0.788
As a continuous variable[8]					1.03(0.92 , 1.14)
Life time abortion					

Never	163	85.34	471	83.51	1.00(ref)
Ever	28	14.66	93	16.49	1.05(0.63 , 1.75)
As a continuous variable[8]					1.21(0.88 , 1.66)
Outcome of first pregnancy[7]					
Live birth	174	93.55	501	91.76	1.00(ref)
Stillbirth	3	1.61	18	3.3	0.61(0.17 , 2.19)
	8	4.30	24	4.40	0.94(0.38 , 2.37)
Ectopic	1	0.54	0	0	NA
Induced	0	0	3	0.55	NA
Number of Ovulatory Cycles					
<=368	68	38.42	230	44.92	1.00(ref)
(368,	59	33.33	155	30.27	0.99(0.63 , 1.56)
>415	50	28.25	127	24.8	1.06(0.66 , 1.72)
P_{trend}					0.814
As a continuous variable(per 13 ovulatory					1.00(0.96 , 1.04)
Exogenous Hormone					
Oral Contraceptive use					
Never	174	92.06	486	88.04	1.00(ref)
Ever	15	7.94	66	11.96	0.82(0.43 , 1.55)

Notation:

1. Odds ratios and 95% confidence intervals adjusted for age (as a continuous variable), smoking status, pack-years of smoking, county of residence, and BMI.
4. Mantel trend test.
5. Additional adjustment for age at menarche (as a continuous variable).
6. Additional adjustment for length of reproductive window.
7. Additional adjustment for age at first birth
8. Absolute number/count as the continuous variable

Table 3-10. Association between genetic risk scores and lung cancer in Aim 1

Index	aOR	miOR
Multigenetic index		
1st tertile: 0-2 (n=222)	1.00(ref)	1.00(ref)
2nd tertile: 3 (n=171)	**2.28(1.38,3.76)**	1.21(0.93,1.57)
3rd tertile: 4-7 (n=171)	**4.57(2.79,7.49)**	**1.51(1.02,2.24)**
Polygenetic risk scores		
1st quartile: 0-0.921 (n=140)	1.00(ref)	1.00(ref)
2nd quantile: 0.922-1.045 (n=143)	1.11(0.61,2.03)	1.03(0.70,1.54)
3rd quantile: 1.045-1.171 (n=140)	**2.27(1.29,3.99)**	1.25(0.89,1.75)
4th quantile: 1.172-1.554 (n=141)	**3.07(1.75,5.40)**	**1.44(1.02,2.03)**

Notations:
1. aOR: adjusted for age, county, smoking status, pack-years of smoking, and BMI;
2. miOR: multiple imputation using MCMC method, based on age, county, smoking status, pack-years of smoking, BMI and family history of lung cancer.

Table 3-11. Joint association between selected SNPs and parity on lung cancer in Jiangsu study

dbSNP no.	Genotype	Parity ≤3	Case/Ctrl	aOR(95%CI)	RERI(95%CI)	ROR(95%CI)
rs2910164	C:C+G:C	No	64/235	1.00(Ref)		
	C:C+G:C	Yes	80/207	1.20 (0.76, 1.87)	-0.68 (-2.24, 0.89)	0.63 (0.25, 1.59)
	G:G	No	21/47	**1.99 (1.05, 3.78)**		
	G:G	Yes	19/44	1.51 (0.76, 3.00)		
rs197412	T:C+C:C	No	34/162	1.00(Ref)		
	T:C+C:C	Yes	58/132	**1.85 (1.07, 3.19)**	**-1.6 (-3.1, -0.1)**	**0.34 (0.16, 0.72)**
	T:T	No	52/121	**2.00 (1.17, 3.43)**		
	T:T	Yes	41/116	1.25 (0.69, 2.25)		
rs2953	T:T+G:T	No	73/264	1.00(Ref)		
	T:T+G:T	Yes	93/238	1.15 (0.76, 1.75)	-0.25 (-2.83, 2.33)	0.83 (0.24, 2.91)
	G:G	No	13/22	2.17 (0.96, 4.89)		
	G:G	Yes	9/16	2.07 (0.79, 5.46)		
rs1126497	C:C	No	50/183	1.00(Ref)		
	C:C	Yes	56/179	0.93 (0.56, 1.54)	0.82 (-0.43, 2.07)	1.59 (0.74, 3.38)
	C:T+T:T	No	37/105	1.58 (0.92, 2.71)		
	C:T+T:T	Yes	43/79	**2.33 (1.30, 4.18)**		
rs3734637	A:C+C:C	No	33/113	1.00(Ref)		
	A:C+C:C	Yes	35/113	0.96 (0.51, 1.80)	0.24 (-0.64, 1.13)	1.19 (0.55, 2.58)
	A:A	No	50/170	1.40 (0.81, 2.42)		
	A:A	Yes	64/140	1.60 (0.91, 2.80)		
rs2230793	A:C+C:C	No	42/148	1.00(Ref)		
	A:C+C:C	Yes	44/143	0.89 (0.51, 1.54)	0.54 (-0.3, 1.38)	1.52 (0.73, 3.17)
	A:A	No	44/133	1.23 (0.73, 2.09)		
	A:A	Yes	57/107	1.66 (0.96, 2.85)		
rs12894467	T:T	No	46/181	1.00(Ref)		
	T:T	Yes	54/157	0.88 (0.52, 1.50)	0.9 (-0.12, 1.93)	1.86 (0.86, 4.06)
	C:T+C:C	No	37/97	1.23 (0.71, 2.13)		
	C:T+C:C	Yes	46/87	**2.01 (1.16, 3.50)**		

Multigenetic	<3	No	15/104	1.00(Ref)		
Index	<3	Yes	23/97	1.50 (0.68, 3.33)	-0.13 (-2.06, 1.8)	0.74 (0.3, 1.79)
	>=3	No	73/184	**3.55 (1.82, 6.94)**		
	<=3	Yes	79/158	**3.93 (1.95, 7.89)**		
Polygenetic	<1.045	No	29/144	1.00(Ref)		
Risk Score	<1.045	Yes	38/125	1.31 (0.70, 2.42)	-0.34 (-1.87, 1.19)	0.76 (0.35, 1.62)
	>1.045	No	60/147	**2.74 (1.57, 4.79)**		
	>1.045	Yes	64/134	**2.71 (1.51, 4.84)**		

Notation: Age (continuous variable), BMI categories, tobacco smoking status, pack-years of smoking, and county of residence were the covariates adjusted for in all multivariable logistic regression models.

Table 3-12. Summary of participating studies in the pooled analysis

Study Name	PI(Institute)	Years of Enrollment	Source of Controls	Study Design	#Cases (%)	#Controls (%)
Genes and Environment in Lung Cancer I (GEL1)	A. Seow (National University of Singapore, Singapore)	1995-1998	Hospital	Case-control	324(14.57)	763(15.64)
Aichi Study	K. Mastuo (Aichi Cancer Center, Japan)	2001–2005	Hospital	Case-control	185(8.32)	185(3.79)
Nanjing Lung Cancer Study (NJLCS)	H. Shen (Nanjing Medical University, China)	2002-2007	Population	Case-control	217(9.76)	456(9.35)
Multiethnic Cohort Study (MEC)	Loïc Le Marchand (University of Hawai‘i, USA)	1993-1996	Population	Nested case-control	499(20.32)	998(18.68)
Singapore Chinese Health Study (SCHS)	J.M. Yuan (University of Pittsburg, USA)	1993-1998	Population	Nested case-control	344(15.77)	688(14.36)
Jiangsu Four Cancers Study (JFC)	J.K. Zhao (Jiangsu CDC, China)	2003-2010	Population	Case-control	887(39.88)	2,252(46.17)
Total					2,456(100%)	5,342(100%)

Table 3-13. Histology and menopausal status

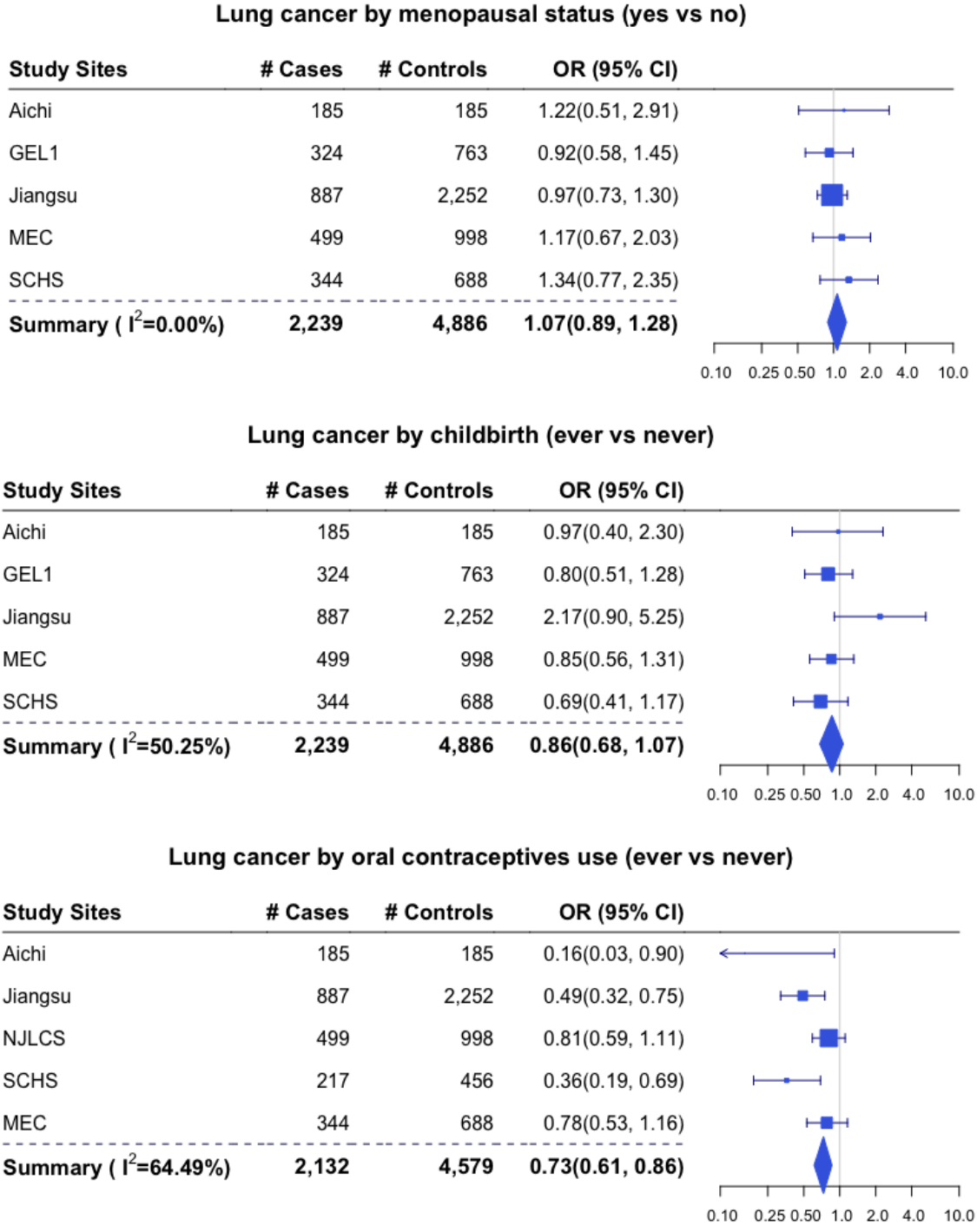
Grouping factors	#Cases (%)	#Controls (%)	*P*-value
Menopause (GEL1, Aichi, NJLCS, MEC, SCHS, Jiangsu)			<0.001
No	310(13.20)	632(12.18)	
Yes	2,039(86.80)	4,557(87.82)	
Missing	107(4.36)	153(2.86)	
Total	2,456	5,342	
Histology (GEL1, Aichi, MEC, SCHS)			<0.001
Without lung cancer	0(0)	2,631(100.00)	
Small cell lung carcinoma	95(7.03)	0(0.00)	
Non-small cell lung cancer			
Squamous cell carcinoma	164(12.13)	0(0.00)	
Adenocarcinoma	736(54.44)	0(0.00)	
Large cell lung carcinoma	69(5.10)	0(0.00)	
Non-small cell carcinoma, mixed/NOS[1]	88(6.51)	0(0.00)	
Carcinoma, mixed/NOS[1]	75(5.55)	0(0.00)	
Other/unclassified lung cancer[2]	125(9.25)	0(0.00)	
Missing	0(0)	0(0.00)	
Total	1,352	2,631	

Notations:
1. NOS: not otherwise specified
2. Other/unclassified lung cancer: carcinoid, adenocarcinoid, carcinosarcoma, hamartoma, blastoma, mesothelioma, epithelioma, etc., unclassified, or no information available.

Table 3-14. Distribution of covariates (All six studies pooled)

		Cases Mean(SD)	**Controls Mean(SD)**	***P*-value**
Age		66.46(12.26)	66.54(12.09)	0.7894
		#Cases(%)	**#Controls(%)**	
Education				**<0.0001**
	Elementary or lower	1529(62.26)	3759(70.37)	
	Secondary	444(18.08)	896(16.77)	
	Post-secondary	200(8.14)	402(7.53)	
	Missing	283(11.52)	285(5.34)	
Country of Origin				**<0.0001**
	Japan	185(7.53)	185(3.46)	
	China	1204(49.02)	2857(53.48)	
	USA	499(20.32)	998(18.68)	
	Singapore	528(21.50)	1152(21.56)	
	Malaysia	33(1.34)	135(2.53)	
	Other Asian	7(0.29)	15(0.28)	
Smoking status				**<0.0001**
	Never	1604(65.31)	4477(83.81)	
	Former	258(10.50)	345(6.46)	
	Current	583(23.74)	495(9.27)	
	Missing	11(0.45)	25(0.47)	
Comprehensive smoking index (CSI)				**<0.0001**
	CSI=0 (non-smokers)	1604(65.31)	4477(83.81)	
	CSI>0 and CSI<0.744	119(4.85)	255(4.77)	
	CSI>=0.744 and CSI<1.312	163(6.64)	199(3.73)	
	CSI>=1.312 and CSI<1743	232(9.45)	154(2.88)	
	CSI>=1.743 and CSI<3.000	234(9.53)	139(2.60)	
	Missing	104(4.23)	118(2.21)	
Pack-year				
	Never smoked	1604(65.39)	4477(83.84)	**<0.0001**
	<10	153(6.24)	271(5.07)	
	10 to <20	189(7.70)	193(3.61)	
	20 to <30	130(5.30)	107(2.00)	
	30 to <40	116(4.73)	77(1.44)	
	40 to <50	72(2.94)	58(1.09)	
	50 to <60	45(1.83)	36(0.67)	
	>=60	59(2.41)	37(0.69)	
	Missing	85(3.47)	84(1.57)	
Family history of lung cancer				**<0.0001**
	No	2265(92.22)	4718(88.32)	
	Yes	153(6.23)	140(2.62)	
	Missing	38(1.55)	484(9.06)	

Figure 3-2. Study-specific odds ratios and confidence intervals for childbirth, menopausal status, and oral contraceptive use



Notation:
1. The odds ratios and 95% confidence intervals for each individual studies and for the combined population were based on unconditional logistic regressions adjusted for age (as a continuous variable), smoking status, CSI (comprehensive smoking index), and family history of lung cancer
2. In the analyses of childbirth, length of reproductive window was additionally adjusted for
3. The size of the bars in the forest plots reflected the inverse variance of individual studies

Table 3-15. Hormonal factors associated with lung cancer

	Cases		Controls		aOR (95% CI)[1]
	N	%	N	%	
Menstrual characteristics					
Age at menarche (GEL1, Aichi, NJLCS, MEC, SCHS, Jiangsu)					
<=14yrs	973	41.53	2,100	40.66	1.00(ref)
15–16yrs	768	32.78	1,678	32.49	**1.16(1.01 , 1.33)**
17+yrs	602	25.69	1,387	26.85	**1.24(1.05 , 1.45)**
Missing		4.60		3.31	
P_{trend}					**0.008**
As a continuous variable					**1.04(1.01 , 1.07)**
Age at menopause(GEL1, Aichi, NJLCS, MEC, SCHS, Jiangsu)[2, 4]					
<=49yrs	976	47.87	2,139	46.94	1.00(ref)
50-54yrs	832	40.80	1,968	43.19	0.91(0.80 , 1.03)
55+yrs	231	11.33	450	9.87	**1.24(1.02 , 1.51)**
Missing		0.00		0.00	
P_{trend}					0.371
As a continuous variable					1.00(0.99 , 1.01)
Menopausal status (Aichi, MEC, SCHS, Jiangsu)					
Premenopausal	222	12.40	492	12.71	0.98(0.79 , 1.23)
Natural menopause	1,338	74.71	3,017	77.96	1.00(ref)
Non-natural menopause	231	12.90	361	9.33	**1.39(1.13 , 1.71)**
Missing		6.48		15.48	
Reproductive window(GEL1, Aichi, NJLCS, MEC, SCHS, Jiangsu)[2]					
>3 and <=31.5 years	667	35.25	1,447	34.30	1.00(ref)
>31.5 and <=35.5	621	32.82	1,346	31.90	1.05(0.91 , 1.22)
>35.5and <50	604	31.92	1,426	33.80	0.89(0.77 , 1.04)
Missing		7.21		7.42	
P_{trend}					0.143
As a continuous variable					0.99(0.98 , 1.01)
Childbearing histories					
Live birth (GEL1, MEC, SCHS, Jiangsu)[3]					
0-2	806	40.10	1,600	34.97	1.00(ref)
3-4	754	37.51	1,861	40.67	**0.82(0.72 , 0.94)**
5+	450	22.39	1,115	24.37	**0.71(0.60 , 0.84)**
Missing		2.14		2.66	
P_{trend}					**0.000**
As a continuous variable					**0.94(0.91 , 0.97)**
Age at 1st delivery (Aichi, GEL1, NJLCS, MEC, SCHS, Jiangsu)[4]					
<20yrs	447	20.41	1,087	22.36	1.00(ref)

21-25yrs	1,231	56.21	2,712	55.78	**1.23(1.06 , 1.43)**
26 yrs or older	512	23.38	1,063	21.86	**1.27(1.06 , 1.52)**
Missing		10.83		8.99	
P_{trend}					**0.010**
As a continuous variable					1.01(1.00-, 1.02)
Outcome of 1st delivery (SCHS, Jiangsu)[5]					
Live birth	1,097	95.64	2,621	95.14	1.00(ref)
Miscarriage/induced abortion	25	2.18	57	2.07	0.70(0.42 , 1.17)
Still birth/ectopic pregnancy	25	2.18	77	2.79	0.99(0.59 , 1.64)
Missing		6.82		6.29	
Exogenous hormone use					
Ever used oral contraceptives(Aichi, NJLCS, MEC, SCHS, Jiangsu)					
No	1,752	88.00	3,716	85.33	1.00(ref)
Yes	239	12.00	639	14.67	**0.69(0.57 , 0.83)**
Missing		6.61		4.89	
Oral contraceptives use status(NJLCS, SCHS, MEC, Jiangsu)					
Never	1,576	87.07	3,542	84.88	1.00(ref)
Former	95	5.25	329	7.88	**0.65(0.49 , 0.85)**
Current	139	7.68	302	7.24	**0.74(0.57 , 0.96)**
Missing		7.04		5.03	
Years of oral contraceptives use (Aichi, NJLCS, SCHS, MEC, Jiangsu)					
As a continuous variable					**0.97(0.95 , 1.00-)**
Missing		7.65		5.92	
Ever used estrogen in HRT (MEC, SCHS, Jiangsu)					
No	1,382	84.42	3,126	84.28	1.00(ref)
Yes	255	15.58	583	15.72	0.86(0.70 , 1.07)
Missing		5.38		5.82	
Estrogen use status (MEC, SCHS, Jiangsu)					
Never	1,382	84.42	3,126	84.28	1.00(ref)
Former	103	6.29	192	5.18	0.97(0.73 , 1.31)
Current	152	9.29	391	10.54	0.80(0.63 , 1.02)
Missing		5.38		5.82	

Notation:
1. The mixed effect logistic regression model is composed of a random intercept of study site and fixed slopes of individual level covariates including age (as a continuous variable), smoking status, CSI (comprehensive smoking index), and family history of lung cancer.
2. Age at menopause was investigated only among post-menopausal women
3. Length of reproductive window was additionally adjusted for
4. Age at menarche was additionally adjusted for
5. Age at first birth was additionally adjusted for

Table 3-16. Hormonal factors associated with lung cancer, by histology

	Controls		Adenocarcinoma			Squamous Cell Carcinoma		
	N	**%**	**N**	**%**	**aOR (95% CI)[1]**	**N**	**%**	**aOR (95% CI)[1]**
Menstrual characteristics								
Age at menarche (GEL1, Aichi, MEC, SCHS)								
<=14yrs	1607	62.55	427	59.97	1.00(ref)	90	56.25	1.00(ref)
15–16yrs	714	27.79	194	27.25	1.10(0.88 , 1.36)	45	28.13	1.09(0.68 , 1.74)
17+yrs	248	9.65	91	12.78	**1.48(1.09 , 2.00)**	25	15.63	1.10(0.57 , 2.14)
Missing	2.47			3.26			2.44	
P_{trend}					**0.021**			0.710
As a continuous variable					**1.08(1.03 , 1.14)**			1.05(0.94 , 1.16)
Age at menopause(GEL1, Aichi, MEC, SCHS)[2,4]								
<=49yrs	1069	46.93	324	50.31	1.00(ref)	84	55.63	1.00(ref)
50-54yrs	991	43.50	261	40.53	0.83(0.68 , 1.02)	59	39.07	0.76(0.50 , 1.15)
55+yrs	218	9.57	59	9.16	0.83(0.59 , 1.18)	8	5.30	0.47(0.19 , 1.14)
Missing	0.00			0.00			0.00	
P_{trend}					0.089			0.053
As a continuous variable					0.98(0.96 , 1.00+)			0.97(0.94 , 1.01)
Menopausal status (binary menopausal reason) (Aichi, MEC, SCHS)								
Premenopausal	183	10.18	58	10.76	0.82(0.54 , 1.24)	5	4.90	0.46(0.15 , 1.40)
Natural menopause	1278	71.12	360	66.79	1.00(ref)	76	74.51	1.00(ref)
Non-natural menopause	336	18.70	121	22.45	**1.45(1.11 , 1.91)**	21	20.59	1.06(0.57 , 1.96)
Missing	3.96			3.75			5.56	
Reproductive window(GEL1, Aichi, MEC, SCHS)[2]								
>=3 and <32 years	625	28.91	196	32.61	1.00(ref)	46	31.94	1.00(ref)
>=32 and <36	571	26.41	182	30.28	0.96(0.75 , 1.23)	56	38.89	1.18(0.72 , 1.92)
>=36 and <50	966	44.68	223	37.10	**0.71(0.56 , 0.89)**	42	29.17	0.62(0.38 , 1.03)
Missing	5.09			6.68			4.64	
P_{trend}					**0.003**			0.065

As a continuous variable					**0.98(0.96 , 0.99)**			0.97(0.94 , 1.01)
Childbearing histories								
Live birth (GEL1, MEC, SCHS)[3]								
0-2	902	37.43	258	44.71	1.00(ref)	53	33.76	1.00(ref)
3-4	805	33.40	191	33.10	0.83(0.65 , 1.04)	46	29.30	0.94(0.57 , 1.55)
5+	703	29.17	128	22.18	**0.60(0.44 , 0.80)**	58	36.94	0.88(0.39 , 2.01)
Missing	1.59			50.64			1.88	
P_{trend}					**0.001**			0.753
As a continuous variable					**0.91(0.86 , 0.96)**			1.00(0.91 , 1.08)
Age at 1st delivery (GEL1, Aichi, MEC, SCHS)[4]								
<20yrs	506	21.96	105	16.72	1.00(ref)	56	38.10	1.00(ref)
21-25yrs	1053	45.70	301	47.93	1.31(0.99 , 1.72)	57	38.78	0.70(0.44 , 1.12)
>=26yrs	745	32.34	222	35.35	**1.51(1.13 , 2.02)**	34	23.13	0.78(0.46 , 1.34)
	12.5							
Missing	3			14.67			10.37	
P_{trend}					**0.006**			0.337
As a continuous variable					1.02(1.00-, 1.03)			1.00(0.96 , 1.05)
Exogenous hormone use								
Ever used oral contraceptives(Aichi, MEC, SCHS)								
No	1428	77.52	454	82.70	1.00(ref)	74	69.16	1.00(ref)
Yes	414	22.48	95	17.30	**0.70(0.52 , 0.93)**	33	30.84	1.08(0.61 , 1.92)
Missing	1.55			1.96			0.93	
Oral contraceptives use status(MEC, SCHS)								
Never	1254	75.54	308	77.00	1.00(ref)	70	67.96	1.00(ref)
Former	138	8.31	27	6.75	0.75(0.47 , 1.21)	13	12.62	2.07(0.89 , 4.81)
Current	268	16.14	65	16.25	**0.66(0.47 , 0.92)**	20	19.42	0.71(0.38 , 1.35)
Missing	1.54			1.48			0.96	
Years of oral contraceptives use (Aichi, MEC, SCHS)								

As a continuous variable					0.99(0.95 , 1.03)			1.02(0.95 , 1.09)
Missing	0.11			2.68			1.85	
Ever used estrogen in HRT (MEC, SCHS)								
No	1089	65.52	266	66.50	1.00(ref)	73	72.28	1.00(ref)
Yes	573	34.48	134	33.50	0.87(0.67 , 1.12)	28	27.72	0.77(0.45 , 1.30)
Missing	1.42			1.48			2.88	
Estrogen use status (MEC, SCHS)								
Never	1089	65.52	266	66.50	1.00(ref)	73	72.28	1.00(ref)
Former	188	11.31	47	11.75	0.86(0.59 , 1.27)	15	14.85	0.95(0.47 , 1.91)
Current	385	23.16	87	21.75	0.87(0.65 , 1.17)	13	12.87	0.64(0.33 , 1.26)
Missing	1.42			1.48			2.88	

Notation:
1. The mixed effect logistic regression model is composed of a random intercept of study site and fixed slopes of individual level covariates including age (as a continuous variable), smoking status, CSI (comprehensive smoking index), and family history of lung cancer.
2. Age at menopause was investigated only among post-menopausal women
3. Length of reproductive window was additionally adjusted for
4. Age at menarche was additionally adjusted for

Table 3-17. Hormonal factors and the risk of lung cancer, by publication status

	Published (Aichi, SCHS, and Jiangsu)					Not published (GEL1, NJLCs, and MEC)				
	Controls		Cases		aOR (95% CI)[1]	Controls		Cases		aOR (95% CI)[1]
	N	%	N	%		N	%	N	%	
Menstrual characteristics										
Age at menarche (GEL1, Aichi, NJLCS, MEC, SCHS, Jiangsu)										
<=14yrs	893	29.56	402	29.41	1.00(ref)	1,164	68.47	515	64.94	1.00(ref)
15–16yrs	1,144	37.87	513	37.53	1.11(0.93 , 1.32)	366	21.53	194	24.46	1.24(0.99 , 1.57)
17+yrs	984	32.57	452	33.07	**1.23(1.02 , 1.48)**	170	10.00	984	10.59	1.28(0.93 , 1.75)
P_{trend}					**0.031**					**0.040**
As a continuous variable					1.02(0.98 , 1.06)					**1.08(1.03 , 1.14)**
Age at menopause (GEL1, Aichi, NJLCS, MEC, SCHS, Jiangsu)[2, 4]										
<=49yrs	1,086	41.72	498	42.31	1.00(ref)	787	52.19	429	58.45	1.00(ref)
50-54yrs	1,237	47.52	514	43.67	0.92(0.79 , 1.08)	574	38.06	252	34.33	0.96(0.78 , 1.19)
55+yrs	280	10.76	165	14.02	**1.52(1.20 , 1.92)**	147	9.75	53	7.22	0.82(0.56 , 1.19)
P_{trend}					**0.026**					0.340
As a continuous variable					**1.02(1.00+, 1.04)**					0.99(0.97 , 1.01)
Menopausal status (Aichi, MEC, SCHS, Jiangsu)										
Premenopausal	412	14.00	192	14.39	1.00(0.78 , 1.28)	80	8.63	30	6.56	0.90(0.51 , 1.59)
Natural menopause	2,451	83.28	1,060	79.46	1.00(ref)	566	61.06	278	60.83	1.00(ref)
Non-natural menopause	80	2.72	82	6.15	**1.92(1.36 , 2.72)**	281	30.31	149	32.60	1.23(0.92 , 1.63)
Reproductive window (GEL1, Aichi, NJLCS, MEC, SCHS, Jiangsu)[2]										
>=3 and <32 years	855	34.50	367	33.12	1.00(ref)	427	30.46	257	38.36	1.00(ref)
>=32 and <36	778	31.40	372	33.57	1.20(0.99 , 1.44)	453	32.31	208	31.04	0.84(0.65 , 1.08)
>=36 and <50	845	34.10	369	33.30	0.98(0.81 , 1.18)	522	37.23	205	30.60	**0.76(0.59 , 0.98)**
P_{trend}					0.896					**0.032**
As a continuous variable					1.01(0.99 , 1.03)					**0.98(0.96 , 1.00-)**
Childbearing histories										
Live birth (GEL1, MEC, SCHS, Jiangsu)[3]										
0-2	846	29.64	429	35.69	1.00(ref)	754	43.79	377	46.66	1.00(ref)
3-4	1,258	44.08	488	40.60	**0.77(0.65 , 0.92)**	603	35.02	266	32.92	0.88(0.70 , 1.11)

5+	750	26.28	285	23.71	**0.68(0.55 , 0.85)**	365	21.20	165	20.42	0.83(0.57 , 1.21)
P_{trend}					**0.000**					0.220
As a continuous variable					**0.93(0.89 , 0.97)**					0.97(0.92 , 1.03)
Age at 1st delivery (Aichi, GEL1, NJLCS, MEC, SCHS, Jiangsu)[4]										
<20yrs	731	24.99	284	21.68	1.00(ref)	291	19.49	148	21.20	1.00(ref)
21-25yrs	1,749	59.79	798	60.92	1.24(1.04 , 1.48)	681	45.61	318	45.56	1.20(0.91 , 1.60)
>=26yrs	445	15.21	228	17.40	1.26(0.99 , 1.59)	521	34.90	232	33.24	**1.44(1.07 , 1.94)**
P_{trend}					**0.037**					**0.014**
As a continuous variable					1.01(0.99 , 1.03)					**1.03(1.00+, 1.05)**
Exogenous hormone use										
Ever used oral contraceptives (Aichi, NJLCS, MEC, SCHS, Jiangsu)										
No	2,660	90.48	1,253	93.09	1.00(ref)	701	72.12	351	72.82	1.00(ref)
Yes	280	9.52	93	6.91	**0.61(0.47 , 0.80)**	271	27.88	131	27.18	0.81(0.59 , 1.11)
Oral contraceptives use status (NJLCS, SCHS, MEC, Jiangsu)										
Never	2,486	90.14	1,077	92.37	1.00(ref)	701	72.12	351	72.82	1.00(ref)
Former	249	9.03	84	7.20	**0.66(0.51 , 0.87)**	3	0.31	0	0.00	NA
Current	23	0.83	5	0.43	0.39(0.13 , 1.17)	268	27.57	131	27.18	0.81(0.59 , 1.12)
Years of oral contraceptives use (Aichi, NJLCS, SCHS, MEC, Jiangsu)										
As a continuous variable					**0.94(0.90 , 0.98)**					1.01(0.97 , 1.04)
Ever used estrogen in HRT (MEC, SCHS, Jiangsu)										
No	2,699	98.68	1,137	98.61	1.00(ref)	427	43.84	245	50.62	1.00(ref)
Yes	36	1.32	16	1.39	1.02(0.56 , 1.88)	547	56.16	239	49.38	0.81(0.63 , 1.05)
Estrogen use status (MEC, SCHS, Jiangsu)										
Never	2,699	98.68	1,137	98.61	1.00(ref)	427	43.84	245	50.62	1.00(ref)
Former	20	0.73	7	0.61	0.80(0.33 , 1.94)	172	17.66	96	19.83	0.87(0.61 , 1.24)
Current	16	0.59	9	0.78	1.29(0.56 , 2.96)	375	38.50	143	29.55	0.78(0.59 , 1.04)

Notation:
1. The mixed effect logistic regression model is composed of a random intercept of study site and fixed slopes of individual level covariates including age (as a continuous variable), smoking status, CSI (comprehensive smoking index), and family history of lung cancer.
2. Age at menopause was investigated only among post-menopausal women
3. Length of reproductive window was additionally adjusted for
4. Age at menarche was additionally adjusted for

Table 3-18. Hormonal factors and the risk of lung cancer, by smoking status

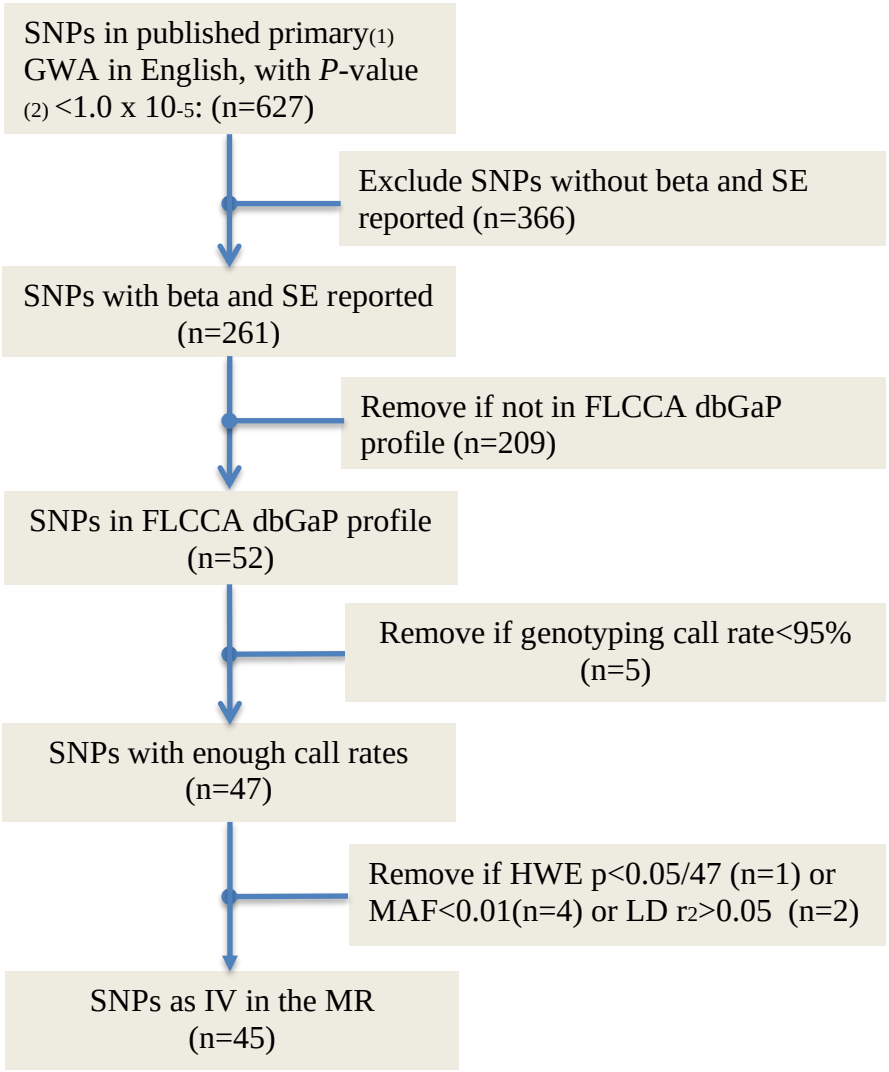
	Smokers					Non-smokers				
	Controls		Cases		aOR (95% CI)[1]	Controls		Cases		aOR (95% CI)[1]
	N	%	N	%		N	%	N	%	
Menstrual characteristics										
Age at menarche (GEL1, Aichi, NJLCS, MEC, SCHS, Jiangsu)										
<=14yrs	346	43.14	382	46.87	1.00(ref)	1,739	40.04	585	38.54	1.00(ref)
15–16yrs	230	28.68	263	32.27	**1.16(1.01 , 1.33)**	1,444	33.25	501	33.00	1.08(0.92 , 1.27)
17+yrs	226	28.18	170	20.86	**1.24(1.05 , 1.45)**	1,160	26.71	432	28.46	**1.26(1.05 , 1.50)**
P_{trend}					**0.008**					**0.014**
As a continuous variable					**1.04(1.01 , 1.07)**					**1.03(1.00+, 1.07)**
Age at menopause(GEL1, Aichi, NJLCS, MEC, SCHS, Jiangsu)[2, 4]										
<=49yrs	367	48.67	443	57.09	1.00(ref)	2,452	54.77	876	54.61	1.00(ref)
50-54yrs	319	42.31	279	35.95	0.91(0.80 , 1.03)	1,643	36.70	551	34.35	0.98(0.85 , 1.13)
55+yrs	68	9.02	54	6.96	**1.24(1.02 , 1.51)**	382	8.53	177	11.03	**1.40(1.13 , 1.73)**
P_{trend}					**0.371**					**0.030**
As a continuous variable					1.00(0.99 , 1.01)					1.02(1.00-, 1.03)
Menopausal status (binary menopausal reason) (Aichi, MEC, SCHS, Jiangsu)										
Premenopausal	41	5.96	40	6.02	0.98(0.79 , 1.23)	450	14.21	182	16.25	0.98(0.76 , 1.25)
Natural menopause	562	81.69	518	78.01	1.00(ref)	2,444	77.20	817	72.95	1.00(ref)
Non-natural menopause	85	12.35	106	15.96	**1.39(1.13 , 1.71)**	272	8.59	121	10.80	**1.63(1.25 , 2.13)**
Reproductive window(GEL1, Aichi, NJLCS, MEC, SCHS, Jiangsu)[2]										
>=3 and <32 years	251	34.91	300	41.27	1.00(ref)	1,192	34.21	362	31.29	1.00(ref)
>=32 and <36	238	33.10	228	31.36	1.05(0.91 , 1.22)	1,100	31.57	391	33.79	1.13(0.94 , 1.35)
>=36 and <50	230	31.99	199	27.37	0.89(0.77 , 1.04)	1,192	34.21	404	34.92	1.03(0.87 , 1.24)
Childbearing histories										
Live birth (GEL1, MEC, SCHS, Jiangsu)[3]										
0-2	259	33.46	306	39.48	1.00(ref)	1,338	35.33	496	40.36	1.00(ref)
3-4	284	36.69	266	34.32	**0.82(0.72 , 0.94)**	1,568	41.40	487	39.63	**0.84(0.72 , 0.99)**
5+	231	29.84	203	26.19	**0.71(0.60 , 0.84)**	881	23.26	246	20.02	**0.80(0.65 , 0.99)**
P_{trend}					**0.000**					**0.023**
As a continuous variable					**0.94(0.91 , 0.97)**					**0.96(0.92 , 1.00-)**

Age at 1st delivery (Aichi, GEL1, NJLCS, MEC, SCHS, Jiangsu)[4]										
<20yrs	235	31.89	214	29.36	1.00(ref)	849	20.67	232	15.97	1.00(ref)
21-25yrs	378	51.29	364	49.93	**1.23(1.06 , 1.43)**	2,322	56.54	862	59.33	**1.21(1.01 , 1.45)**
>=26yrs	124	16.82	151	20.71	**1.27(1.06 , 1.52)**	936	22.79	359	24.71	**1.26(1.02 , 1.57)**
P_{trend}					**0.010**					**0.036**
As a continuous variable					1.01(1.00-, 1.02)					1.01(0.99 , 1.02)
Outcome of 1st delivery (SCHS, Jiangsu)[5]										
Live birth	367	91.75	299	96.14	1.00(ref)	2,254	95.71	798	95.45	1.00(ref)
Miscarriage/induced abortion	15	3.75	6	1.93	0.70(0.42 , 1.17)	42	1.78	19	2.27	0.78(0.44 , 1.37)
Still birth/ectopic pregnancy	18	4.50	6	1.93	0.99(0.59 , 1.64)	59	2.51	19	2.27	1.28(0.74 , 2.22)
Exogenous Hormone use										
Ever used oral contraceptives(Aichi, NJLCS, MEC, SCHS, Jiangsu)										
No	561	79.91	561	81.66	1.00(ref)	3,144	86.40	1,184	91.29	1.00(ref)
Yes	141	20.09	126	18.34	**0.69(0.57 , 0.83)**	495	13.60	113	8.71	**0.70(0.54 , 0.89)**
Oral contraceptives use status(NJLCS, SCHS, MEC, Jiangsu)										
Never	529	79.19	519	80.59	1.00(ref)	3,002	85.99	1,050	90.60	1.00(ref)
Former	32	4.79	25	3.88	**0.65(0.49 , 0.85)**	297	8.51	70	6.04	**0.71(0.52 , 0.97)**
Current	107	16.02	100	15.53	**0.74(0.57 , 0.96)**	192	5.50	39	3.36	0.70(0.47 , 1.04)
Years of oral contraceptives use (Aichi, NJLCS, SCHS, MEC, Jiangsu)										
As a continuous variable					**0.97(0.95 , 1.00-)**					**0.94(0.90 , 0.98)**
Ever used estrogen in HRT (MEC, SCHS, Jiangsu)										
No	514	77.76	487	76.33	1.00(ref)	2,603	85.82	891	89.91	1.00(ref)
Yes	147	22.24	151	23.67	0.86(0.70 , 1.07)	430	14.18	100	10.09	**0.71(0.56 , 0.90)**
Estrogen use status (MEC, SCHS, Jiangsu)										
Never	514	77.76	487	76.33	1.00(ref)	2,603	85.82	891	89.91	1.00(ref)
Former	44	6.66	66	10.34	0.97(0.73 , 1.31)	144	4.75	34	3.43	0.71(0.48 , 1.05)
Current	103	15.58	85	13.32	0.80(0.63 , 1.02)	286	9.43	66	6.66	**0.71(0.53 , 0.95)**

Notation:

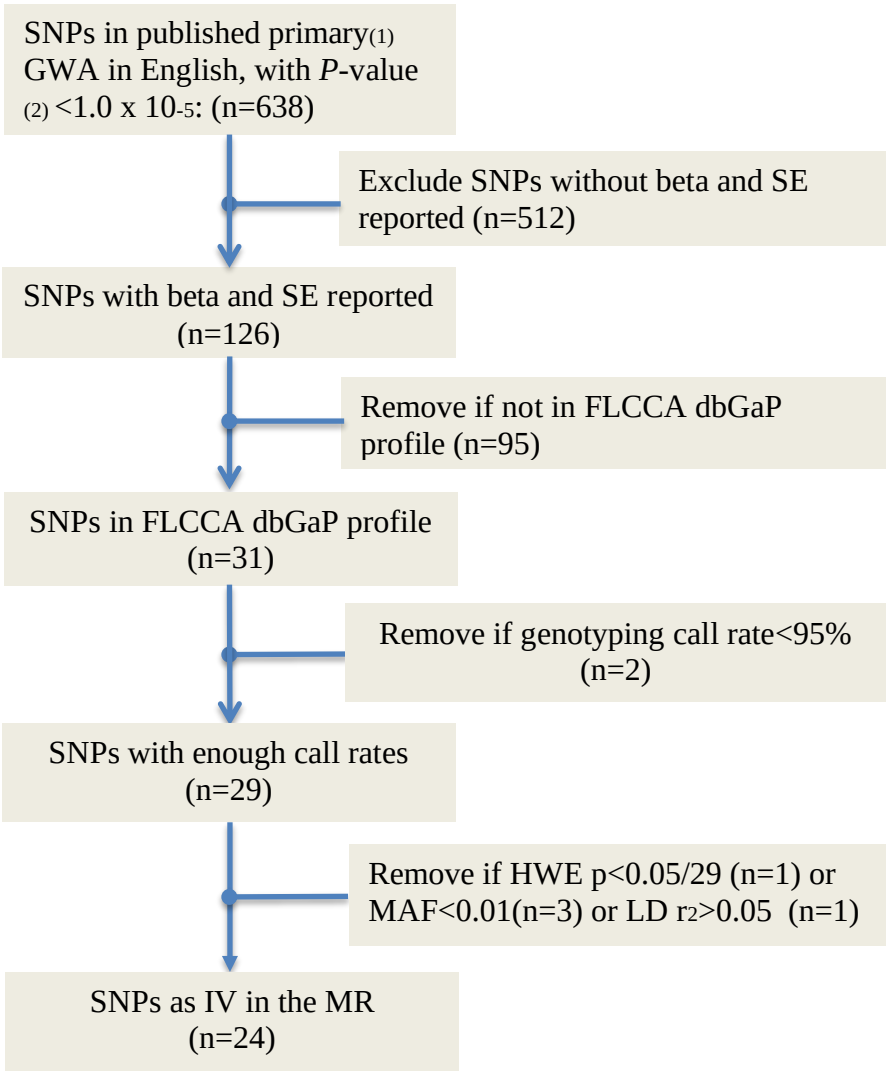
1. The mixed effect logistic regression model is composed of a random intercept of study site and fixed slopes of individual level covariates including age (as a continuous variable), smoking status, CSI (comprehensive smoking index), and family history of lung cancer.
2. Age at menopause was investigated only among post-menopausal women
3. Length of reproductive window was additionally adjusted for
4. Age at menarche was additionally adjusted for
5. Age at first birth was additionally adjusted for

Figure 3-3. IV SNPs selection for age at menarche



Notation:
(1) Primary GWA analysis: array-based genotyping and analysis of 100,000+ pre-QC SNPs selected to tag variation across the genome and without regard to gene content
(2) Statistical significance <1.0 × 10-5: SNP-trait *P*-value <1.0 × 10-5 in the overall (initial GWA + replication) population. If a study did not report a combined *P*-value, the *P*-value and effect size from the largest sample size was be reported as long as the initial and replication samples each showed an association of a *P*-value < 1.0 × 10-5. If a study did not include a replication stage, significant SNPs from the discovery stage were reported.

Figure 3-4. IV SNPs selection for age at menopause



Notation:
(1) Primary GWA analysis: array-based genotyping and analysis of 100,000+ pre-QC SNPs selected to tag variation across the genome and without regard to gene content
(2) Statistical significance <1.0 × 10-5: SNP-trait *P*-value <1.0 × 10-5 in the overall (initial GWA + replication) population. If a study did not report a combined *P*-value, the *P*-value and effect size from the largest sample size was be reported as long as the initial and replication samples each showed an association of a *P*-value < 1.0 × 10-5. If a study did not include a replication stage, significant SNPs from the discovery stage were reported.

Figure 3-5. Linkage Disequilibrium between Selected SNPs for Menarche MR

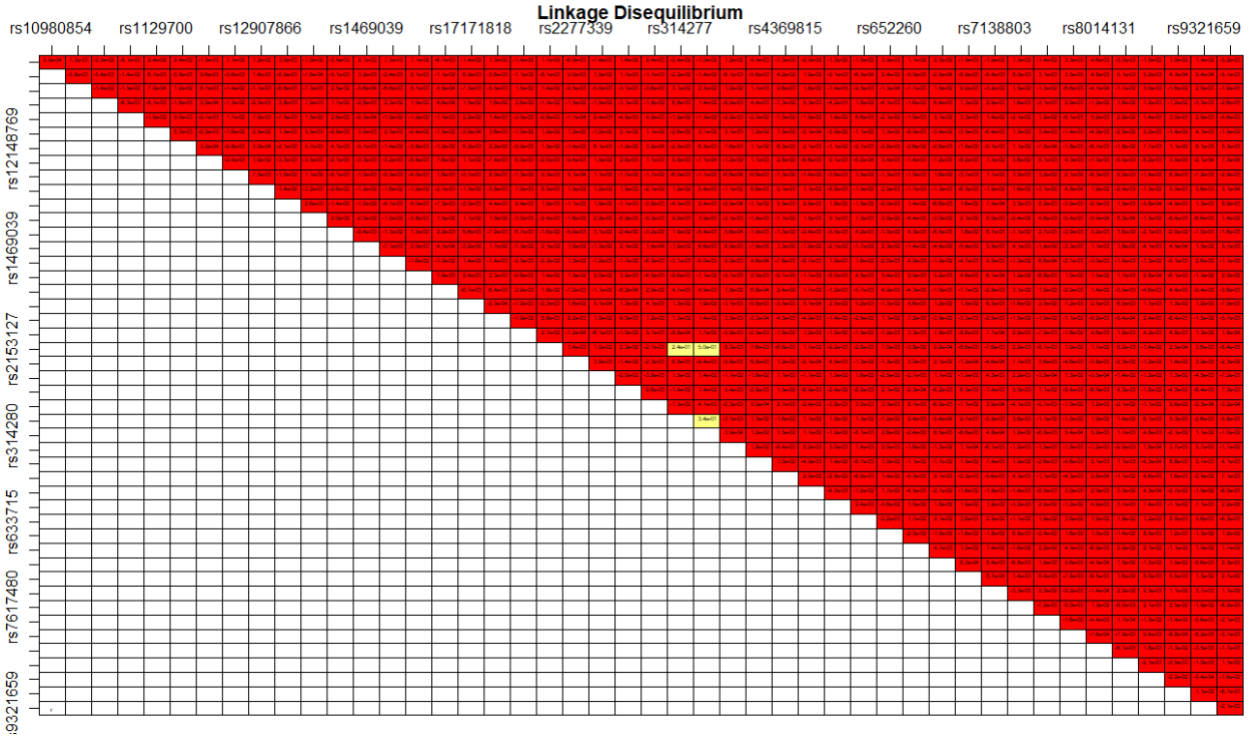


Figure 3-6. Linkage Disequilibrium between Selected SNPs for Menopause MR

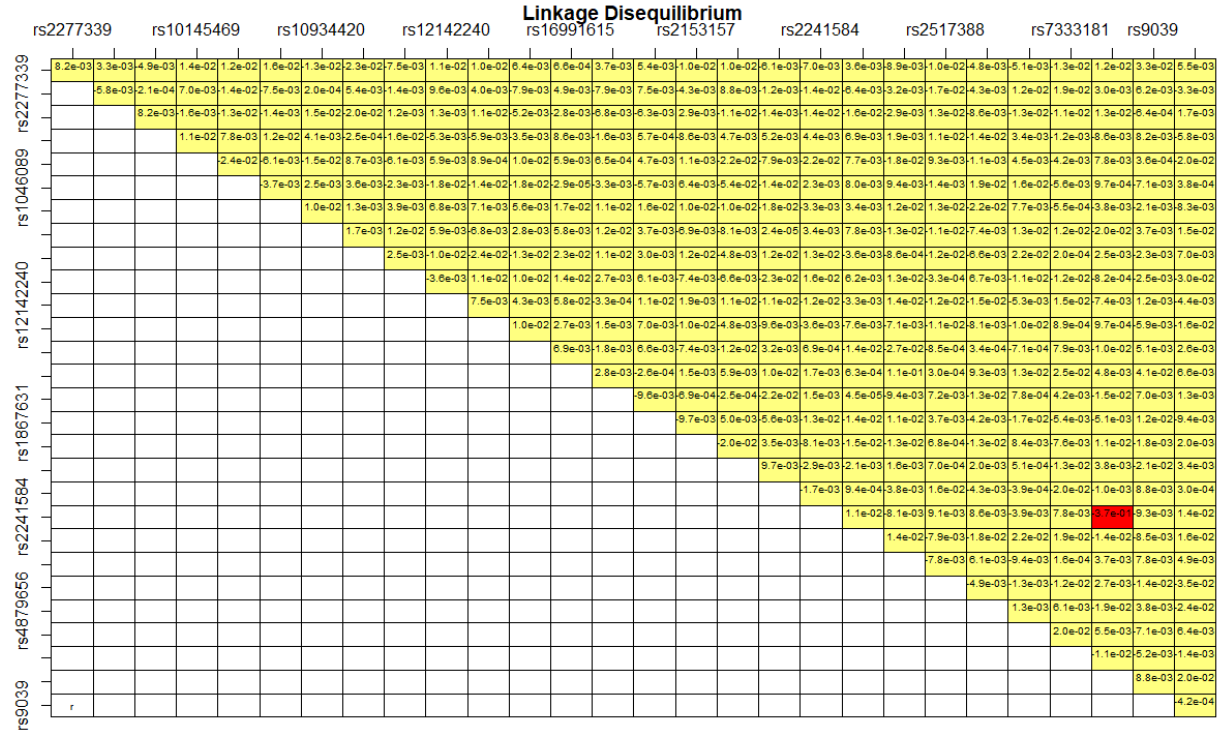


Table 3-19. SNPs used as IVs for menarche, identified from published primary GWA studies

No.	SNP and risk allele	PubMed ID	Chromosome location	Mapped genes	Type of variant	Risk allele freq	*P*-value	β	95% CI
1	rs10423674-A	25231870	19p13.11	CRTC1	intron variant	0.34	9.00E-12	0.04	[0.03-0.05] unit increase
2	rs10980854-A	25231870	9q31.3	AL162414.1 - OR2K2	regulatory region variant	0.06	1.00E-08	0.06	[0.038-0.082] unit increase
3	rs11071033-T	23599027	15q21.3	UNC13C	intron variant	0.71	3.00E-06	4.49	[2.61-6.37] unit increase
4	rs11165924-A	25231870	1p21.3	DPYD	intron variant	0.69	2.00E-09	0.03	[0.018-0.042] unit increase
5	rs11216435-T	23599027	11q23.3	DSCAML1	intron variant	0.32	3.00E-06	4.41	[2.55-6.27] unit increase
6	rs1129700-T	25231870	16p11.2	KCTD13, ASPHD1	3'-UTR variant	0.44	2.00E-09	0.03	[0.02-0.04] unit increase
7	rs12148769-G	25231870	15q11.2	RNU6-741P - PWRN4	intergenic variant	0.9	5.00E-11	0.05	[0.034-0.066] unit increase
8	rs12472911-C	25231870	2q22.1	LRP1B	intron variant	0.2	7.00E-10	0.04	[0.028-0.052] unit increase
9	rs12907866-A	23599027	15q21.2	CYP19A1, MIR4713HG	intron variant	0.84	4.00E-07	6.06	[3.71-8.41] unit increase
10	rs13196561-C	25231870	6q16.3	AL080285.1 - SIM1	intergenic variant	0.78	8.00E-12	0.04	[0.028-0.052] unit increase
11	rs1324913-G	25231870	13q22.1	KLF12 - LINC00402	intergenic variant	0.65	3.00E-10	0.03	[0.02-0.04] unit increase
12	rs1364063-C	25231870	16q22.1	CYB5B - NFAT5	intergenic variant	0.43	6.00E-21	0.05	[0.04-0.06] unit increase
13	rs1469039-A	25231870	8q24.3	KCNK9	intron variant	0.19	4.00E-12	0.05	[0.036-0.064] unit increase
14	rs16896742-G	25231870	6p22.1	HLA-A - HLA-W	Intron variant	0.38	3.00E-10	0.04	[0.028-0.052] unit increase
15	rs16918636-T	25231870	11p14.1	AC090833.1 - AC090791.1	intergenic variant	0.79	3.00E-08	0.03	[0.018-0.042] unit increase

16	rs17171818-C	25231870	5q31.2	KDM3B	intron variant	0.77	9.00E-14	0.04	[0.028-0.052] unit increase
17	rs1799949-G	29773799	17q21.31	BRCA1	synonymous variant	0.661 4	3.00E-08	0.15 2	[0.099-0.205] year decrease
18	rs1915146-G	25231870	10q26.13	CTBP2 NPHP3-AS1 -	intron variant	0.4	4.00E-08	0.03	[0.02-0.04] unit increase
19	rs2600959-A	25231870	3q22.1	AC079942.1	intergenic variant	0.34	4.00E-11	0.04	[0.03-0.05] unit increase
20	rs2688325-T	25231870	8p23.2	CSMD1	intron variant	0.29	2.00E-09	0.03	[0.018-0.042] unit increase
21	rs3101336-T	25231870	1p31.1	NEGR1 - RPL31P12	regulatory region variant	0.4	5.00E-13	0.04	[0.03-0.05] unit increase
22	rs314280-T	19448622	6q16.3	LIN28B	intron variant	0.48	2.00E-14	1.2	[0.9-1.5] months increase
23	rs365132-G	29773799	5q35.2	UIMC1	synonymous variant	0.493 6	9.00E-13	0.19 2	[0.14-0.24] year decrease
24	rs3743266-T	25231870	15q22.2	RORA-AS1, RORA	3'-UTR variant	0.68	2.00E-13	0.04	[0.03-0.05] unit increase
25	rs5762534-T	29773799	22q12.1	TTC28	intron variant	0.822 2	6.00E-06	0.15 5	[0.088-0.222] year decrease
26	rs6009583-C	25231870	22q13.33	Z82202.1 - AC207130.1	intergenic variant	0.74	5.00E-08	0.03	[0.018-0.042] unit increase
27	rs633715-C	21102462	1q25.2	LINC01741 - SEC16B	intergenic variant	0.2	2.00E-08	2.6	[1.62-3.58] week decrease
28	rs652260-T	25231870	19p13.2	EVI5L	intron variant	0.54	1.00E-08	0.03	[0.02-0.04] unit increase
29	rs6747380-A	25231870	2p16.1	CCDC85A, AC007744.1	intron variant	0.17	6.00E-28	0.07	[0.056-0.084] unit increase
30	rs6933660-C	25231870	6q25.1	ARMT1 - CCDC170	intergenic variant	0.69	1.00E-09	0.03	[0.02-0.04] unit increase
31	rs7114467-A	23667675	11p15.2	INSC - RF00324	intergenic variant	0.459 57	9.00E-06	0.07 13	[0.040-0.103] year decrease
32	rs7138803-G	25231870	12q13.12	BCDIN3D - AC131157.1	intergenic variant	0.62	2.00E-12	0.04	[0.03-0.05] unit increase
33	rs7642134-G	25231870	3p12.1	AC108706.1 - VGLL3	intergenic variant	0.61	3.00E-16	0.04	[0.03-0.05] unit increase

34	rs7861820-C	19448621	9q31.2	LINC01505	intron variant	0.48	3.00E-09	0.09	[0.06-0.12] years decrease
35	rs8014131-A	23599027	14q31.3	AL049775.2	intron variant	0.42	3.00E-07	4.61	[2.85-6.37] unit decrease
36	rs8050136-C	25231870	16q12.2	FTO	intron variant	0.6	2.00E-17	0.04	[0.03-0.05] unit increase
37	rs852069-G	25231870	20p12.1	RF00012 - RNU6-27P	intergenic variant	0.64	1.00E-13	0.04	[0.03-0.05] unit increase
38	rs913588-G	25231870	9p24.1	KDM4C	missense variant	0.49	6.00E-11	0.03	[0.02-0.04] unit increase
39	rs9321659-A	25231870	6q16.2	RF00019 - MCHR2	intergenic variant	0.13	3.00E-16	0.06	[0.044-0.076] unit increase
40	rs988913-C	25231870	6p12.1	FAM83B	intron variant	0.66	1.00E-12	0.04	[0.03-0.05] unit increase

Table 3-20. SNPs used as IVs for menopause, identified from published primary GWA studies

No.	SNP and risk allele	PubMed ID	Chromosome location	Mapped genes	Type of variant	Risk allele freq	*P*-value	β	95% CI
1	rs10145469-C	29773799	14q32.2	AL158800.1 - LINC02325	intergenic variant	0.8157	3.00E-09	0.068	[0.046-0.09] year increase
2	rs1046089-A	22267201	6p21.33	PRRC2A, PRRC2A, PRRC2A, PRRC2A, PRRC2A, PRRC2A	missense variant	0.353	2.00E-16	0.213	[0.16-0.26] years decrease
3	rs10852344-T	26414677	16p13.13	GSPT1 - AC007216.5	intergenic variant	0.59	1.00E-15	0.16	[0.12-0.2] years decrease
4	rs10934420-T	29773799	3q13.32	AC092691.1	intron variant	0.3657	7.00E-07	0.045	[0.027-0.063] year decrease
5	rs11031006-G	26414677	11p14.1	AL358944.1 - FSHB	intergenic variant	0.85	9.00E-14	0.22	[0.16-0.28] years decrease
6	rs1172822-T	19448621	19q13.42	BRSK1	intron variant	0.37	2.00E-19	0.49	[0.38-0.60] years decrease

7	rs12461110-A	26414677	19q13.43	NLRP11	missense variant	0.35	8.00E-16	0.17	[0.13-0.21] years decrease
8	rs1411478-A	26414677	1q25.3	STX6	intron variant	0.41	1.00E-10	0.13	[0.091-0.169] years decrease
9	rs1713460-G	26414677	14q11.2	PIP4P1 - PNP	intergenic variant	0.3	2.00E-10	0.14	[0.1-0.18] years decrease
10	rs1799949-G	26414677	17q21.31	BRCA1	synonymous variant	0.68	8.00E-11	0.14	[0.1-0.18] years decrease
11	rs1867631-A	23307926	1p31.3	SGIP1	intron variant	0.2892	5.00E-06	0.1071	[0.060-0.154] years decrease
12	rs2153157-A	22267201	6p24.2	AL024498.2, SYCP2L	intron variant	0.492	8.00E-12	0.165	[0.12-0.21] years increase
13	rs2230365-C	26414677	6p21.33	NFKBIL1, NFKBIL1, NFKBIL1, NFKBIL1, NFKBIL1, NFKBIL1	synonymous variant	0.84	8.00E-10	0.17	[0.11-0.23] years decrease
14	rs2236553-C	26414677	20q13.33	SLCO4A1	intron variant	0.24	6.00E-10	0.16	[0.1-0.22] years decrease
15	rs2241584-A	26414677	5q35.2	RNF44	stop gained	0.38	2.00E-11	0.14	[0.1-0.18] years decrease
16	rs2307449-G	22267201	15q26.1	POLG	intron variant	0.405	4.00E-13	0.184	[0.14-0.23] years decrease
17	rs2517388-G	22267201	8p11.23	ASH2L	intron variant	0.174	9.00E-15	0.262	[0.2-0.33] years increase
18	rs365132-G	26414677	5q35.2	UIMC1	synonymous variant	0.51	1.00E-33	0.24	[0.2-0.28] years decrease
19	rs4879656-A	26414677	9p21.1	APTX	intron variant	0.37	2.00E-08	0.12	[0.081-0.159] years decrease
20	rs5762534-T	26414677	22q12.1	TTC28	intron variant	0.84	6.00E-09	0.16	[0.1-0.22] years decrease

21	rs6495785-A	24045676	15q14	DPH6-DT	intron variant	0.787	5.00E-06	0.69	[0.40-0.98] unit decrease
22	rs7333181-A	19448619	13q34	TEX29 - AL359649.1	intergenic variant	0.12	3.00E-08	0.52	[0.34-0.70] years increase
23	rs9039-C	26414677	16p13.2	C16orf72, AC087190.3	3'-UTR variant	0.28	3.00E-08	0.12	[0.081-0.159] years decrease
24	rs930036-A	26414677	2q31.1	TLK1	intron variant	0.38	3.00E-19	0.19	[0.15-0.23] years decrease

Table 3-21. Phenotype information in FLCCA (Step 2)

Phenotype	**Levels**	**Case N(Column %)**	**Control N(Column %)**	***P*-value**
Age	<40	250 (5.1)	290 (7.3)	<0.001
	[40, 50)	742 (15.1)	594 (15.0)	
	[50, 60)	1,470 (29.9)	1,242 (31.4)	
	[60, 70)	1,617 (32.9)	1,287 (32.5)	
	>=70	843 (17.1)	546 (13.8)	
Histology	Adenocarcinoma	3,595 (73.0)		<0.001
	Squamous cell carcinoma	660 (13.4)		
	Other	667 (13.6)		
	Control		3,959 (100.0)	
Total	(N=8,881)	N=4,922	N=3,959	

Table 3-22. Effects of ages at menarche and menopause on lung cancer among East Asians

	MR Methods	Menarche		Menopause	
		OR(95% CI)	***P*-Value**	**OR(95% CI)**	***P*-Value**
Two-sample Mendelian randomization	Inverse-variance weighted method	1.03(0.87,1.21)		1.02(0.87,1.21)	
	Maximum likelihood method	1.03(0.87,1.22)		1.02(0.95,1.10)	
	Weighted median-based method	0.93(0.74,1.17)		0.99(0.74,1.17)	
	MR-Egger method	0.93(0.69,1.27)		1.04(0.69,1.27)	
	Intercept, not odds ratio	*0.008(-0.014, 0.031)*	0.460	*-0.006(-0.035, 0.024)*	0.695
Polygenic risk score-based analysis		1.03(0.89,1.19)		1.02(0.96,1.09)	
Stratified polygenetic risk score-based analysis	Adenocarcinoma	0.99(0.84,1.16)		1.03(0.96,1.11)	
	Squamous cell carcinoma	1.08(0.80,1.44)		0.98(0.86,1.11)	

Figure 3-7. Two-sample method: scatterplot of SNP-exposure associations on SNP-outcome associations for age at menarche on lung cancer risk

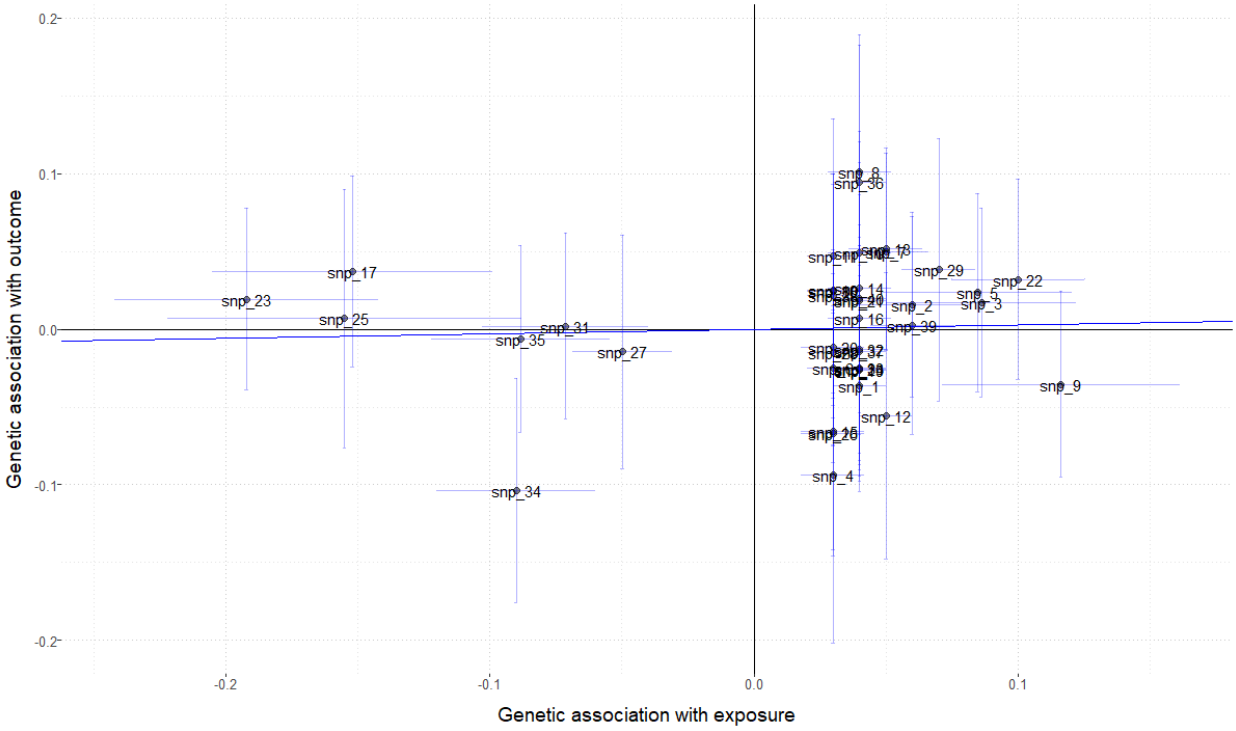


Figure 3-8. Two-sample method: association of menarche and the risk of lung cancer by different MR methods

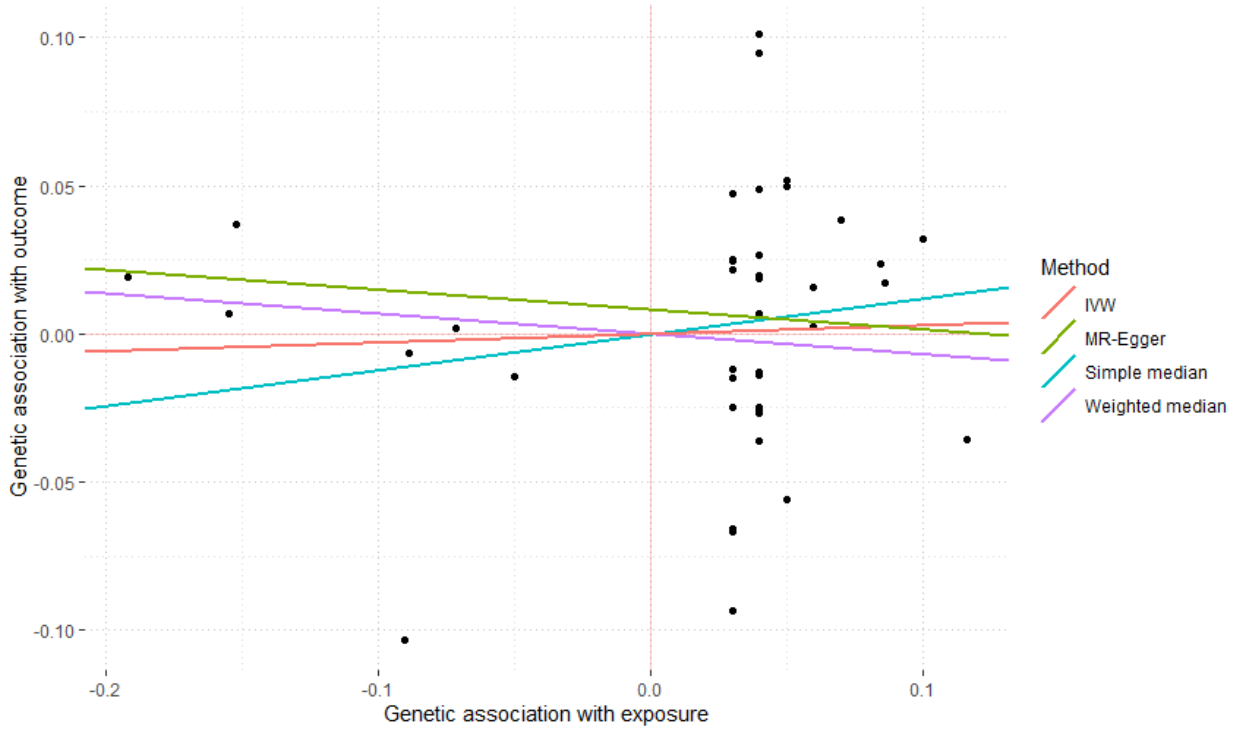


Figure 3-9. Two-sample method: scatterplot of SNP-exposure associations on SNP-outcome associations for age at menopause on lung cancer risk

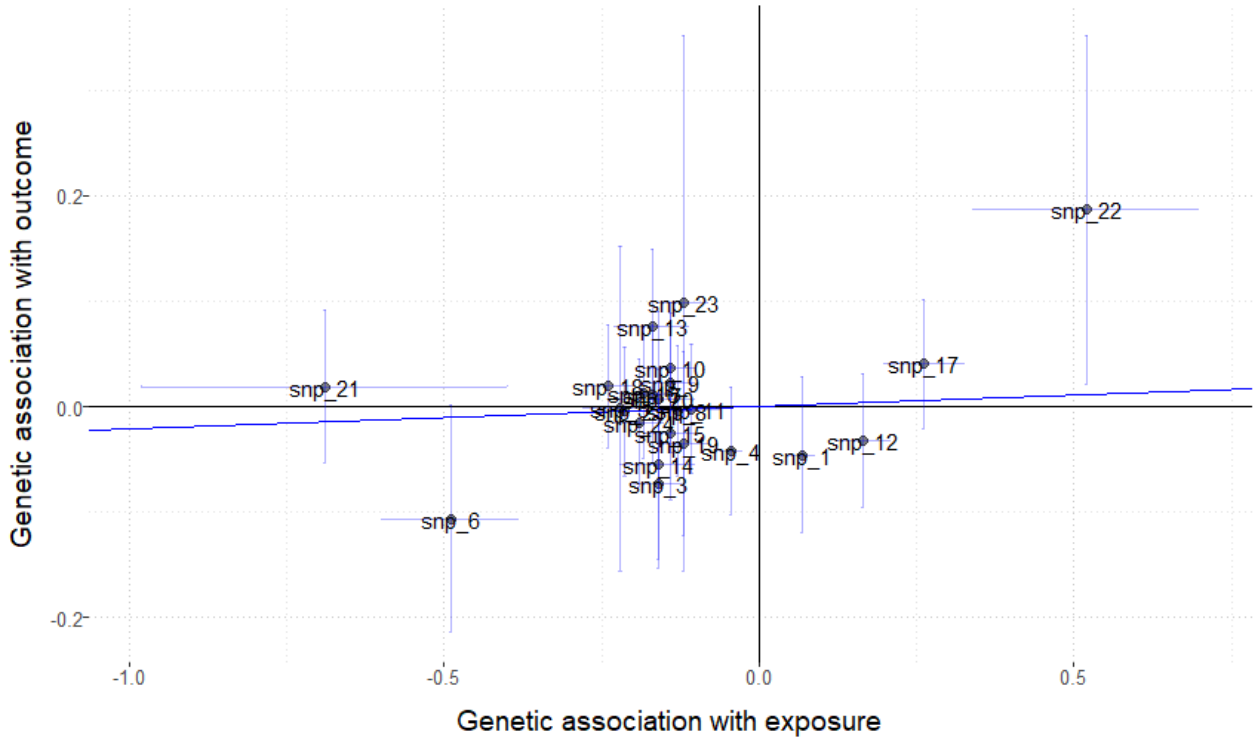
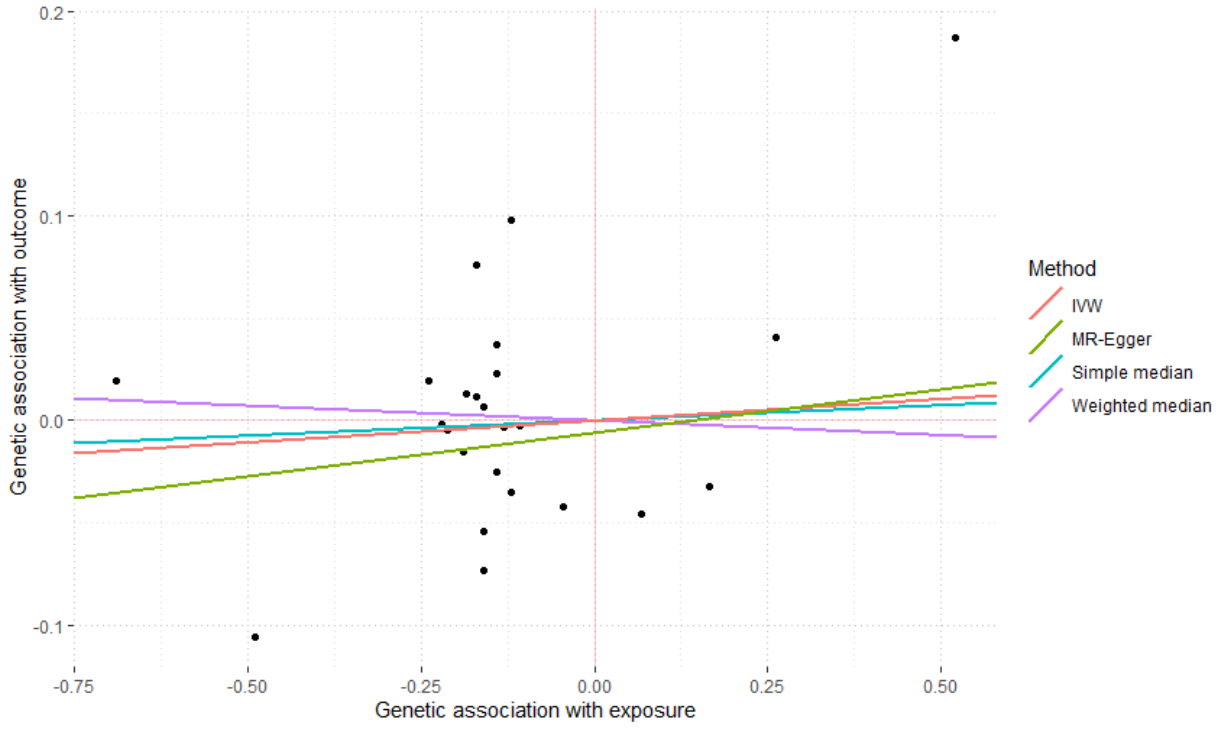


Figure 3-10. Two-sample method: association of menopause and the risk of lung cancer by different MR methods



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