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Association between family history with lung cancer incidence and mortality risk in the Asia Cohort Consortium

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Abstract

Family history of lung cancer (FHLC) has been widely studied but most prospective cohort studies have primarily been conducted in non-Asian countries. We assessed the association between FHLC with risk of lung cancer (LC) incidence and mortality in a population of East Asian individuals. A total of 478,354 participants from 11 population-based cohorts in the Asia Cohort Consortium were included. A Cox proportional hazards regression model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). A total of 7,785 LC incident cases were identified. FHLC (any LC subtype) was associated with an increased risk of LC incidence (HR = 1.45, 95% CI = 1.30–1.63). The positive association was observed in men and women (HR = 1.44, 95% CI = 1.26–1.66 in men; HR = 1.47, 95% CI = 1.22–1.79 in women), and in both never-smokers and ever-smokers (HR = 1.43, 95% CI = 1.18–1.73 in never-smokers; HR = 1.46, 95% CI =1.27–1.67 in ever-smokers). FHLC was associated with an increased risk of lung adenocarcinoma (HR = 1.63, 95% CI: 1.36–1. 94), squamous cell carcinoma (HR = 1.88, 95% CI: 1.46–2.44), and other non-small cell LC (HR = 1.94, 95% CI: 1.02–3.68). However, we found no evidence of significant effect modification by sex, smoking status, and ethnic groups. In conclusion, FHLC was associated with increased risk of LC incidence and mortality, and the associations remained consistent regardless of sex, smoking status and ethnic groups among the East Asian population.

KEYWORDS
Asia, cohort consortium, family history, lung cancer

What's new?

Studies looking at family history of lung cancer have mostly been conducted outside of Asia. Here, the authors evaluated the relationship between family history of lung cancer and lung cancer incidence and mortality in East Asian populations. Using data collected from nearly half a million people, they showed that family history was positively associated with incidence and mortality of the disease in both men and women, regardless of smoking status or ethnic background. These results indicate the importance of considering family history as part of screening and prevention strategies.

1 | INTRODUCTION

Lung cancer (LC) is the most frequently diagnosed cancer and leading cause of cancer mortality worldwide, accounting for over 2.5 million new cases (12.4% of the total cancer cases) and 1.8 million deaths (18.7% of the total cancer death) in 2022.[1,2] The incidence and mortality of LC are highest in Asia as compared to Europe and the United States, with 60% of new LC cases and 62% of all LC-related deaths occurring in Asia.[3] The risk factors for LC include but are not limited to, cigarette smoking, passive smoking, air pollution, and personal history of lung disease.[4] It is well-established that family history is one of the risk factors for lung cancer, particularly among never-smokers.[3]

Previous case–control and cohort studies have shown that a family history of LC (FHLC) in first-degree relatives, early onset of LC among relatives, and multiple affected family members are significantly associated with an increased risk of LC.[5] A recent meta-analysis suggested that the association between familial risk of LC and LC risk may vary by ethnicity and sex. For example, the familial risk of squamous cell lung carcinoma was greater in Asians as compared to Western populations.[5] However, most longitudinal studies have been conducted in Europe and North America, and evidence from Asia is limited.[5] There was only one prospective cohort study involving Asian individuals that examined the familial association by histological subtype of LC, however, due to insufficient sample size, the conclusions regarding LC subtypes were unclear.[6]

In this study, we assessed the association between FHLC with LC incidence and mortality using a pooled analysis of 11 prospective cohort studies in East Asians that included approximately half a million participants from the Asia Cohort Consortium (ACC).

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2 | METHODS

2.1 | Study population

The ACC has been previously described in detail.[7,8] Briefly, the ACC comprises 45 cohort studies conducted from the 1980s to the 2020s and was established to investigate the association between genetics, environmental exposures, lifestyle factors, and the risk of various disease including cancer and cardiovascular disease among Asians. The cohorts provided only baseline questionnaire data and follow-up health outcomes via linkage to disease registries.

A total of 11 cohorts (6 in Japan, 3 in Korea, and 2 in China) with baseline studies conducted from 1984 to 2014 participated in this analysis. All the participating cohorts provided information on FHLC and potential confounders obtained from their baseline questionnaires as well as follow-up LC incidence and mortality. Of 526,839 participants, we excluded 48,485 participants from this analysis who had missing information on FHLC in first-degree relatives, LC incidence, follow-up durations, sex, smoking status, as well as participants with any type of cancer diagnosis at baseline and/or implausible BMI (<10, >100 kg/m^2; Table S1). Ultimately, we included a total of 478,354 participants in our final analysis.

2.2 | Assessment of FHLC

A FHLC was defined as having a first-degree relative (parents, siblings, and children) with LC. However, because LC information in children was not collected in the Japan Public Health Center-Based Prospective Study II (JPHC II), Miyagi Cohort Study (Miyagi), and Ohsaki National Health Insurance Cohort Study (Ohsaki), a FHLC in these studies was defined as having parents and siblings with LC. In the Three-Prefecture Miyagi Cohort (3 Pref Miyagi), only FHLC in parents was collected, therefore, this cohort was excluded from the main analysis and was only included in the sensitivity analyses stratified by FHLC in fathers or mothers (Table S2).

2.3 | Outcome assessment

Identification of incident LC cases and LC deaths for each cohort was conducted through linkage with the respective regional or national cancer registries based on the International Classification of Diseases (ICD) (ICD-9 codes: 162 and ICD-10 codes: C34.0–C34.9). The histological subtype of LC was classified into adenocarcinoma (8140/3, 8260/3, 8480/3, 8250/3, 8253/3), squamous cell carcinoma (8070/3), other non-small cell carcinoma (8012/3, 8046/3), small cell carcinoma (8041/3), and others by the International Classification of Diseases for Oncology (ICD-O-3).

2.4 | Statistical analysis

Person-years of follow-up were calculated from the date of enrollment into the cohort to the date of death for deceased participants, while for living participants, it extends until the date of last contact or the study end. Deaths from other causes or loss to follow-up were treated as censored. Similarly, person-years of follow-up to LC incidence were calculated from the date of enrolment into the cohort until the date of first diagnosis of LC or censoring, whichever occurred first.

Cox proportional hazards models were used to estimate the pooled hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between FHLC with LC incidence and mortality risk. All models were stratified by cohorts and adjusted for sex, age at baseline (continuous, years), cumulative exposure to smoking pack-years (continuous), and alcohol consumption (never, ever). Analyses were then further stratified by sex (men or women), country (China, Japan, or Korea), smoking status (never-smokers or ever-smokers), type of relatives (fathers or mothers), and cohort. We used multivariable imputation to impute missing data on alcohol consumption and smoking pack-years using covariates such as sex, year of study enrolment, follow-up duration, LC status, and mortality based on previous studies[9] using the SAS PROC MI procedure.[10] Potential effect modification by sex (men and women), country (China, Japan, Korea), and smoking status (never, ever) was assessed by adding a product term in the model. To reduce potential confounding by passive smoking, we performed a sensitivity analysis using the five cohort studies (JPHC I, JPHC II, JACC, KNCC, and Namwon) that collected information on passive smoking (never, ever) by further adjusting for passive smoking in the model. All analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC, USA). All statistical tests were two-sided, and p-values <.05 were regarded as statistically significant.

3 | RESULTS

Out of a total of 478,354 participants, with a median follow-up period of 15.0 years, we identified 7,785 incident primary LC cases and 6,163 LC deaths. Approximately 3.5% of participants ($n = 16,743$) reported a FHLC in a first-degree relative. The median age at baseline was 54.0 years, with an interquartile range (IQR) of 16 years. The prevalence of ever-smokers at baseline was 39.9% (Table 1).

Overall, a FHLC in first-degree relatives was significantly associated with an increased risk of LC incidence (HR = 1.45, 95% CI = 1.30–1.63), and the positive association remained consistent across men (HR = 1.44, 95% CI = 1.26–1.66) and women (HR = 1.47, 95% CI = 1.22–1.79; Figure 1). There was no significant interaction by sex (p for interaction = .80), country (p for interaction = .44), or smoking status (p for interaction = .62).

Regarding the age of LC diagnosis, similar positive associations were observed among participants with a LC diagnosis age of below 60, 60, to 70, 70 years or older (diagnosed age <60, HR = 1.75, 95% CI: 1.39–2.21; 60–70, HR = 1.59, 95% CI: 1.32–1.92; >70, HR = 1.30, 95% CI: 1.09–1.55). Furthermore, a higher risk of FHLC incidence was observed among those with first-degree LC history from their fathers (HR = 1.37, 95% CI = 1.16–1.63), mothers (HR = 1.33, 95% CI = 1.02–1.74), and siblings (HR = 1.61, 95%

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TABLE 1 Characteristics of participants in the 11 included cohorts from the Asia Cohort Consortium.

Cohort	SMHS	SWHS	JPHC I	JPHC II	JACC	Miyagi	Ohsaki	3 Pref Miyagi	KMCC	KNCC	Namwon	Total
Country	China	China	Japan	Japan	Japan	Japan	Japan	Japan	Korea	Korea	Korea	
No. of subjects, *N*	61,463	73,339	41,934	54,893	78,172	39,790	41,996	21,942	20,023	34,627	10,175	478,354
No. of incident lung cancer cases, *N*	1145	975	940	1367	767	945	688	147	396	201	214	7785
No. of lung cancer deaths, *N*	956	719	541	909	1210	628	560	115	329	36	160	6163
Years of study entry	2001–2006	1996–2000	1990–1992	1993–1994	1998–1990	1990	1994	1984	1993–2004	2002–2014	2004–2007	1984–2007
No. of women, *N* (%)	NA	73,339 (100.0)	21,717 (51.8)	28,692 (52.3)	43,743 (56.0)	17,825 (44.8)	19,584 (46.6)	11,648 (59.8)	11,979 (59.8)	16,435 (47.5)	6206 (61.0)	251,168 (52.5)
Duration of follow–up years (incidence), median (IQR)	12.2 (11.2–13.5)	18.1 (17.2–18.8)	23.5 (22.7–23.8)	20.3 (17.0–20.8)	19.4 (10.6–21.0)	24.6 (20.8–24.6)	13.2 (9.5–13.2)	15.0 (7.3–15.0)	13.9 (10.9–17.4)	9.0 (6.5–11.9)	12.9 (12.0–14.0)	15.0 (11.7–20.4)
Duration of follow–up years (death), median (IQR)	12.2 (11.2–13.5)	18.1 (17.2–18.8)	22.6 22.3–23.8)	19.7 (18.9–19.8)	19.4 (10.7–21.0)	24.6 (20.8–24.6)	13.2 (9.8–13.2)	15.0 (7.4–15.0)	13.9 (10.9–17.4)	9.0 (6.5–12.0)	12.9 (12.0–14.0)	15.5 (11.9–19.8)
Age range at baseline, years	40–75	40–71	40–59	40–69	40–79	40–64	40–80	40–98	15–91	16–84	45–75	15–91
Age at baseline (years), median (IQR)	53.2 (47.5–63.5)	50.3 (44.4–60.9)	50.0 (44.0–55.0)	54.0 (46.0–62.0)	57.0 (49.0–64.0)	52.0 (44.0–58.0)	61.0 (52.0–68.0)	55.0 (48.0–65.0)	56.0 (45.0–64.0)	49.0 (43.0–56.0)	62.6 (55.5–67.9)	54.0 (46.0–62.0)
Body mass index, kg/m^2, median (IQR)	23.7 (21.6–25.7)	23.7 (21.6–26.1)	23.4 (21.5–25.4)	23.2 (21.4–25.3)	22.6 (20.8–24.6)	23.4 (21.5–25.4)	23.3 (21.4–25.4)	22.9 (21.1–25.0)	23.4 (21.3–25.6)	23.7 (21.8–25.7)	24.3 (22.3–26.4)	23.5 (21.4–25.4)
Smoking status, *N* (%)												
Never smoker	18,662 (30.4)	71,297 (97.2)	24,990 (59.6)	32,812 (59.8)	47,926 (61.3)	19,846 (49.9)	21,547 (51.3)	12,257 (57.1)	12,640 (63.1)	18,499 (53.4)	6722 (66.1)	287,468 (60.1)
Ever smoker	42,801 (69.6)	2042 (2.8)	16,944 (40.4)	22,081 (40.2)	30,246 (38.7)	19,944 (50.1)	20,449 (48.7)	9415 (42.9)	7383 (36.9)	16,128 (46.6)	3453 (33.9)	190,886 (39.9)
Passive smoking[a], *N* (%)	NA	NA	33,217 (79.6)	43,934 (80.9)	43,002 (83.1)	NA	NA	NA	NA	12,912 (57.3)	6777 (68.2)	139,752 (77.6)
Family history of lung cancer in a first-degree relative, *N* (%)	3629 (5.9)	3562 (4.9)	880 (2.1)	973 (1.8)	1828 (2.3)	227 (0.6)	1710 (4.1)	750 (3.4)	238 (1.2)	2617 (7.6)	329 (3.2)	16,743 (3.5)

Abbreviations: 3 Pref Miyagi, Three-Prefecture Miyagi Cohort; IQR, interquartile range; JACC, Japan Collaborative Cohort Study; JPHC, Japan Public Health Center-based prospective Study; KMCC, Korean Multi-center Cancer Cohort Study; KNCC, Korean National Cancer Center Cohort; Miyagi, Miyagi Cohort; *N*, number; NA, not available; Namwon, The Namwon Study; Ohsaki, Ohsaki National Health Insurance Cohort Study; SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study.
[a]Only five cohorts collected data on passive smoking: JPHC I, JPHC II, JACC, KNCC, and Namwon.

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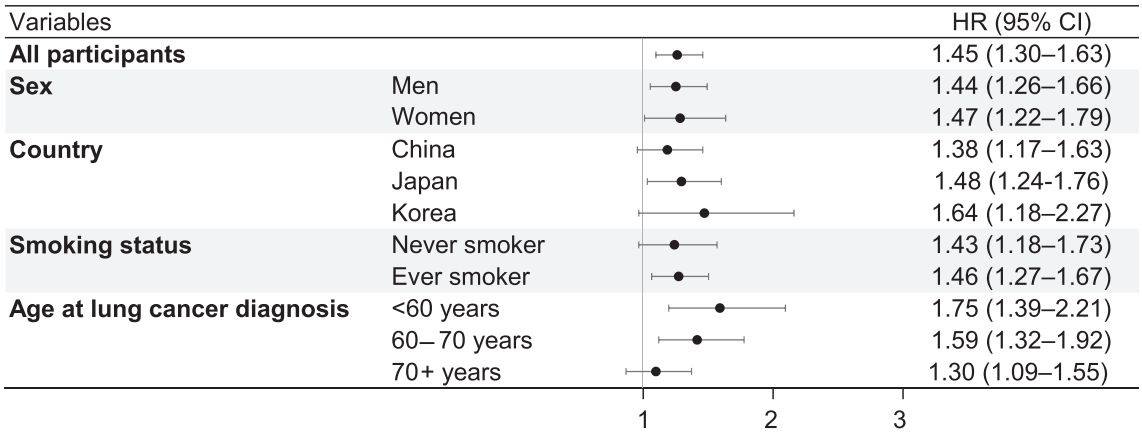

FIGURE 1 Forest plots of the association between family history and the risk of lung cancer incidence, stratified by sex, country, smoking status, and age at lung cancer diagnosis. CI, confidence interval; HR, hazard ratio.

CI = 1.33–1.94), as compared to participants without FHLC in their first-degree relatives (Table 2). Stratification by both the type of first-degree relatives with FHLC and sex revealed that FHLC in siblings was significantly associated with an increased risk of LC incidence in both men (HR = 1.54, 95% CI = 1.22–1.94) and women (HR = 1.78, 95% CI = 1.29–2.46). In addition, FHLC in fathers was significantly associated with LC in men (HR =1.47, 95% CI = 1.20–1.81) and FHLC in mothers was significantly associated with LC in women (HR = 1.66, 95% CI = 1.11–2.49; Table S3 and Figure 2). In sensitivity analyses, the results remained consistent when further stratified by first-degree relative types into fathers and mothers and including cohorts with information only on FHLC in fathers and mothers (Table S4). FHLC in both first-degree male (fathers and brothers) and female relatives (mothers and sisters) was also significantly associated with risk of LC incidence (Table S5).

After stratifying by LC subtypes, FHLC was significantly associated with an increased risk of lung adenocarcinoma (HR = 1.63, 95% CI: 1.36–1.94), squamous cell carcinoma LC (HR = 1.88, 95% CI: 1.46–2.44), and other non-small cell LC incidence (HR = 1.94, 95% CI: 1.02–3.68). However, FHLC was not significantly associated with the risk of small cell carcinoma LC incidence (HR = 1.16, 95% CI = 0.72–1.86; Table 3).

When stratified by country, FHLC was significantly associated with LC incidence risk in both never-smokers and ever-smokers in China (HR = 1.30, 95% CI = 1.02–1.67 in never-smokers, HR = 1.47, 95% CI = 1.17–1.83 in ever-smokers) and Japan (HR = 1.51, 95% CI = 1.08–2.11 in never-smokers, HR = 1.45, 95% CI = 1.19–1.78 in ever-smokers). In Korea, FHLC was significantly associated only with LC incidence among never-smokers (HR = 2.19, 95% CI = 1.23–3.88). A FHLC in fathers (HR = 1.38, 95% CI = 1.11–1.73), mothers (HR = 1.46, 95% CI = 1.04–2.05), and siblings (HR = 1.44, 95% CI = 1.07–1.95) was significantly associated with LC incidence in China, while in Japan, FHLC in fathers (HR = 1.52, 95% CI = 1.13–2.04) and siblings (HR = 1.63, 95% CI = 1.22–2.17) was significantly associated, and in Korea, only FHLC in siblings (HR = 2.17, 95% CI = 1.36–3.44) was significantly associated with LC incidence (Table S6). When further stratified by both country and sex, FHLC in first-degree relatives was significantly associated with risk of LC incidence among men (HR = 1.49, 95% CI = 1.20–1.83) in China, among women (HR = 2.19, 95% CI = 1.23–3.88) in Korea, and among both men (HR = 1.39, 95% CI = 1.13–1.71) and women (HR = 1.72, 95% CI = 1.26–2.35) in Japan.

When stratified by both sex and smoking status, LC risk for FHLC among smoking women (HR = 1.87, 95% CI: 1.10–3.15) was higher than the risk of LC among never smoking women (HR = 1.43, 95% CI: 1.16–1.75; Table S7). The significant association was stronger for FHLC in mothers (HR = 3.30, 95% CI = 1.22–8.90 among smoking women; HR = 1.61, 95% CI = 1.06–2.46 among never smoking women; Tables S8 and S9). Among men, FHLC in fathers was significantly associated with the risk of LC incidence among smoking men (HR = 1.50, 95% CI = 1.22–1.84).

Similar to LC incidence, having FHLC in first-degree relatives was significantly associated with an increased risk of LC mortality (adjusted HR = 1.26, 95% CI = 1.09–1.44; Tables S10 and S11). The association between FHLC and LC mortality risk was similar for both men and women (Table S12). In addition, the association between FHLC with risk of LC incidence and mortality was similar after further adjusting for pack–years of cigarette smoking and passive smoking (Table S13). Cohort-specific results are similar to the overall results (Table S14). Tests for the assumption of proportional hazards using the Schoenfeld residual test[11] showed no evidence for deviation from the proportional-hazards assumption (p-value = .75).

4 | DISCUSSION

In this pooled analysis of 11 prospective cohorts consisting of almost half a million participants in East Asia, we found significant associations between first-degree FHLC with an increased risk of LC incidence and mortality, and that the overall associations were consistent across sex, smoking status, and ethnic groups.

Consistent with our findings, previous cohort studies in China[12,13] and Japan[6] have reported a positive association between FHLC and risk of LC incidence. Similar results were reported in a

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TABLE 2 Associations between family history of lung cancer and risk of lung cancer incidence.

		Incident lung cancer cases with family history of lung cancer		Age- and sex-adjusted model		Fully adjusted model		
				Family history of lung cancer		Family history of lung cancer		
	Total person-years	No	Yes	No	Yes HR (95% CI)	No	Yes HR (95% CI)	*p*-value for interaction[a]
All participants	7,117,859	7315	323	REF	**1.47 (1.31–1.64)**	REF	**1.45 (1.30–1.63)**[b]	
Sex								
Men	3,131,192	5016	213	REF	**1.47 (1.28–1.68)**	REF	**1.44 (1.26–1.66)**[c]	.80
Women	3,986,668	2299	110	REF	**1.48 (1.22–1.79)**	REF	**1.47 (1.22–1.79)**[c]	
Country								
China	2,006,708	1969	151	REF	**1.39 (1.18–1.64)**	REF	**1.38 (1.17–1.63)**[b]	.44
Japan	4,389,269	4575	132	REF	**1.49 (1.25–1.77)**	REF	**1.48 (1.24–1.76)**[b]	
Korea	721,883	771	40	REF	**1.70 (1.23–2.38)**	REF	**1.64 (1.18–2.27)**[b]	
Smoking status								
Never-smoker	4,500,634	2403	115	REF	**1.43 (1.18–1.72)**	REF	**1.43 (1.18–1.73)**[d]	.62
Ever-smoker	2,617,225	4912	208	REF	**1.47 (1.28–1.69)**	REF	**1.46 (1.27–1.67)**[b]	
Age at lung cancer diagnosis, years								
<60	7,117,859	1094	78	REF	**1.80 (1.42–2.26)**	REF	**1.75 (1.39–2.21)**[b]	
60–70	7,117,859	2383	116	REF	**1.62 (1.34–1.95)**	REF	**1.59 (1.32–1.92)**[b]	
70+	7,117,859	3838	129	REF	**1.30 (1.09–1.55)**	REF	**1.30 (1.09–1.55)**[b]	
Passive smoking[e]								
Ever	2,367,180	2434	82	REF	**1.49 (1.19–1.85)**	REF	**1.48 (1.18–1.84)**[b]	.86
Never	617,505	578	16	REF	1.45 (0.88–2.40)	REF	1.37 (0.83–2.27)[b]	
Type of first–degree relatives[f]								
Father	5,030,819	4795	135	REF	**1.40 (1.18–1.66)**	REF	**1.37 (1.16–1.63)**[b]	
Mother	5,030,819	4875	55	REF	**1.34 (1.03–1.75)**	REF	**1.33 (1.02–1.74)**[b]	
Siblings	5,030,819	4819	111	REF	**1.62 (1.34–1.95)**	REF	**1.61 (1.33–1.94)**[b]	

Note: Bolded information denotes statistically significant different with p < 0.05. All models are stratified by cohorts.
Abbreviations: CI, confidence interval; HR, hazard ratio; REF, reference.
[a]Chi-square test (product term) was used to test for interaction.
[b]Models were adjusted for age, sex, pack-years of cigarette smoking, and alcohol consumption.
[c]Models were adjusted for age, pack-years of cigarette smoking, and alcohol consumption.
[d]Models were adjusted for age, sex, and alcohol consumption.
[e]Passive smoking data were only available in five cohorts: JPHC I, JPHC II, JACC, KNCC, and Namwon.
[f]Type of first-degree relatives data was only available in seven cohorts: SMHS, SWHS, JPHC I, JACC, Ohsaki, KNCC, and Namwon.

cohort study in Taiwan[14] and a case–control study in Singapore.[15] In addition, cohort studies conducted in Western countries such as the United States, United Kingdom, and Sweden reported that a FHLC was associated with an increased risk of LC incidence.[5] A recent meta-analysis of 66 case–control and 19 cohort studies[5] showed that a FHLC was significantly associated with an increased risk of LC, and the association was stronger in the Asian population compared to Western populations: Asia (34 studies; pooled summary estimate [PSE] = 2.14, 95% CI = 1.83–2.50), North America (25 studies; PSE = 1.91, 95% CI = 1.65–2.20), Europe (18 studies; PSE = 1.59, 95% CI = 1.41–1.79), Oceania (1 study; PSE = 1.35, 95% CI = 0.29–6.28), and South America (1 study; PSE = 1.21, 95% CI = 0.50–2.92). Similarly, a pooled analysis of 24 case–control studies[16] reported that the association between having a FHLC in a first-degree relative and LC incidence varied by ethnicity, and the associations were strongest in the Asian population (odds ratio [OR] = 2.38, 95% CI = 1.50–3.82), as compared to African Americans (OR = 1.67, 95% CI = 1.16–2.40), and Whites (OR = 1.46, 95% CI = 1.46–1.58). Further large-scale international comparative studies are needed to evaluate and compare family risk of LC across different countries and regions. A previous cohort study of never-smoking women in China found no significant association between FHLC and LC risk.[17] However, the results should be cautiously interpreted given the limited sample size and short follow-up duration. In a more recent cohort study of never-smoking Chinese women, FHLC was reported to be significantly associated with LC risk.[13]

The type of relative and the sex of the relative with a family history of cancer may influence the risks of various cancers in different ways.[19]

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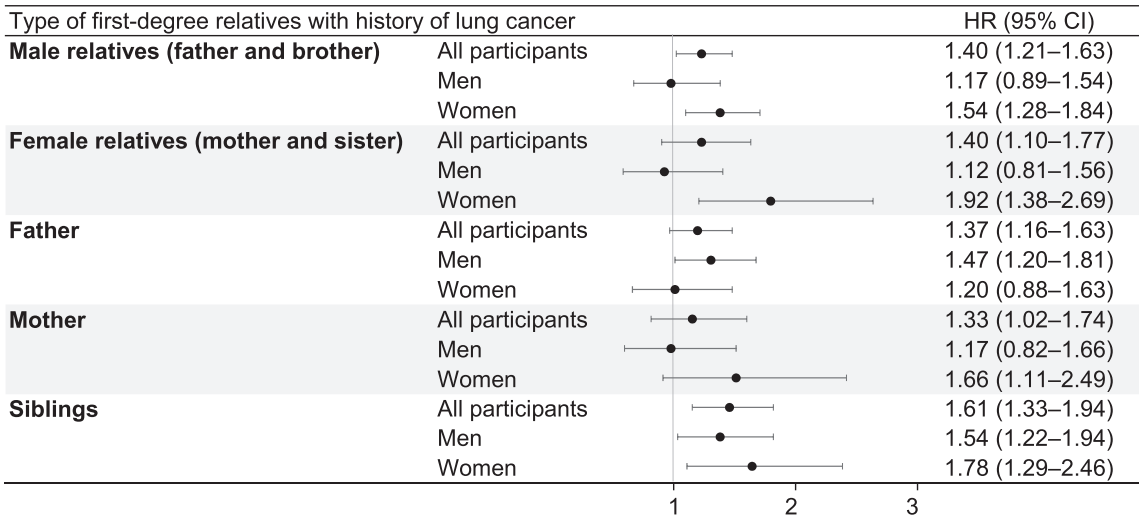

FIGURE 2 Forest plots of the association between family history and the risk of lung cancer incidence, stratified by type of relatives and sex. CI, confidence interval; HR, hazard ratio.

For breast cancer, family history showed similar associations regardless of whether the affected relative was a mother or sister.[20] Conversely, for colorectal cancer, the risk was higher when siblings were affected as compared to parents.[21] Our study suggests that FHLC in siblings is associated with a higher risk of LC incidence than that in fathers and mothers, although this interaction was not statistically significant. Stronger associations between familial history in siblings and LC risk could be attributed to both shared lifestyle habits and genetic factors. Smoking, a major risk factor for LC, often spreads from siblings and parents due to their shared environment from childhood to adolescence. This transmission of smoking habits, along with genetic predisposition, may help explain the higher risk observed in siblings. Parental smoking has been shown to strongly influence children's smoking behaviors.[22] Similarly, siblings also play a significant role in smoking initiation and progression, with parents and siblings having comparable odds of influencing the initial transition to smoking initiation at 32% and 29%,[23] respectively. Previous case–control studies in Asia have reported mixed findings regarding whether the strongest LC risk is associated with FHLC in siblings[24] or parents.[25,26] However, two previous prospective cohort studies conducted in Japan[6] and among never-smoking Chinese women[17] found that the familial risk of LC incidence was the highest among siblings, which aligns with our findings. In our study, FHLC in both male and female first-degree relatives was significantly associated with LC incidence, but there was no significant difference in LC risk between male and female relatives. This contrasts with a case–control study in China, which found higher LC risk in female relatives with FHLC, potentially due to environmental factors like smoky coal use and cooking habits, which are risk factors for LC in Chinese women.[27] However, in our study, when stratified by country, we did not find a significant difference in LC risk between male and female relatives with FHLC in China. Similarly, a cohort study in the United States also found no significant difference in risk between having at least one female versus one male first-degree relative with LC.[28]

In our study, there was no significant interaction by sex in the overall analysis, however, there were significant differences between men and women in the stratified analysis on the association between FHLC in mothers and risk of LC incidence in ever-smokers (p for interaction = .01). A recent meta-analysis found that the familial risk of LC was similar in both sexes in Western countries (pooled HR = 1.74 in women; pooled HR = 1.70 in men), but the LC risk was significantly higher in women compared to men in Asia (pooled HR = 2.42 in women; pooled HR = 1.90 in men)[5] and the trend of higher risk of LC among Asian women compared to men is consistent with our results. However, a pooled analysis of case–control studies in the International Lung Cancer Consortium (ILCCO) found no significant effect modification by sex.[16] FHLC in mothers was significantly associated with risk of LC incidence in ever-smoking women, but not in ever-smoking men. A prior study reported that exposure of mothers to smoking during childhood and adolescence was correlated with the smoking habits of mothers and daughters, and the relationship was reported to be stronger for daughters than for sons.[18] Differences in the transmission of smoking habits from mothers may explain this finding.

We found FHLC to be significantly associated with risk of adenocarcinoma, squamous cell carcinoma, and other non-small cell LC incidence and mortality. However, we did not find a significant association between FHLC with risk of small cell lung carcinoma incidence and mortality, which may be due to the small sample size in this subtype and therefore, limited statistical power. We reported for the first time that FHLC was significantly associated with risk of lung adenocarcinoma in a large prospective cohort study. Previous case–control studies reported that FHLC was associated with increased risk of lung adenocarcinoma[29,30] and squamous cell carcinoma.[30,31] Another pooled analysis of case–control studies reported a positive association between familial risk and risk of LC for all histologic types including adenocarcinoma, squamous cell carcinoma, and small cell carcinoma.[16]

In our study, the association between FHLC and risk of LC incidence and mortality decreased with increasing age in the group aged ≥60 years. The observed trend of reduced risk of LC diagnosis with

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TABLE 3 Association between family history of lung cancer and risk of lung cancer incidence, stratified by lung cancer subtypes.

	Adenocarcinoma		Squamous cell carcinoma		Other non-small cell		Small cell carcinoma		Others/Unknown	
	Family history of lung cancer		Family history of lung cancer		Family history of lung cancer		Family history of lung cancer		Family history of lung cancer	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Person-years	7,064,211		7,050,951		7,039,158		7,043,020		7,068,402	
Incident lung cancer cases	2448	132	1285	62	217	10	588	18	2770	101
Age-, sex-adjusted HR (95% CI)	REF	**1.66 (1.39–1.99)**	REF	**1.90 (1.47–2.46)**	REF	**1.96 (1.03–3.72)**	REF	1.17 (0.73–1.87)	REF	1.17 (0.96–1.43)
Fully adjusted HR (95% CI)[a]	REF	**1.63 (1.36–1.94)**	REF	**1.88 (1.46–2.44)**	REF	**1.94 (1.02–3.68)**	REF	1.16 (0.72–1.86)	REF	1.17 (0.96–1.43)
Sex										
Men										
Incident lung cancer cases	1300	73	1177	59	181	7	529	16	1829	58
Fully adjusted HR (95% CI)[b]	REF	**1.69 (1.34–2.15)**	REF	**1.96 (1.50–2.55)**	REF	1.62 (0.76–3.47)	REF	1.14 (0.70–1.85)	REF	1.06 (0.82–1.38)
Women										
Incident lung cancer cases	1148	59	108	3	36	3	59	2	948	43
Fully adjusted HR (95% CI)[b]	REF	**1.56 (1.20–2.03)**	REF	1.06 (0.34–3.38)	REF	**3.56 (1.07–11.80)**	REF	1.57 (0.38–6.49)	REF	1.36 (0.996–1.84)
Smoking status										
Never-smokers										
Incident lung cancer cases	1263	68	97	2	36	4	41	1	966	40
Fully adjusted HR (95% CI)[c]	REF	**1.59 (1.25–2.04)**	REF	0.75 (0.18–3.06)	REF	4.94 **(1.72–14.24)**	REF	1.03 (0.14–7.56)	REF	1.20 (0.87–1.65)
Ever-smokers										
Incident lung cancer cases	1185	64	1188	60	181	6	547	17	1811	61
Fully adjusted HR (95% CI)[a]	REF	**1.67 (1.30–2.16)**	REF	**1.94 (1.49–2.52)**	REF	1.35 (0.60–3.07)	REF	1.14 (0.70–1.85)	REF	1.14 (0.86–1.48)
Country										
China										
Incident lung cancer cases	778	68	176	23	10	0	78	10	927	50
Fully adjusted HR (95% CI)[a]	REF	**1.56 (1.21–1.99)**	REF	**2.20 (1.42–3.40)**	REF	–	REF	**2.14 (1.11–4.14)**	REF	1.03 (0.78–1.37)
Japan										
Incident lung cancer cases	1460	45	937	31	175	8	416	7	1587	41
Fully adjusted HR (95% CI)[a]	REF	**1.55 (1.15–2.08)**	REF	**1.75 (1.22–2.51)**	REF	**2.25 (1.10–4.59)**	REF	0.85 (0.40–1.80)	REF	1.34 (0.98–1.83)
Korea										
Incident lung cancer cases	210	19	172	8	32	2	94	1	263	10
Fully adjusted HR (95% CI)[a]	REF	2.41 (1.50–3.86)	REF	1.71 (0.83–3.53)	REF	**1.96 (0.45–8.49)**	REF	0.39 (0.05–2.86)	REF	1.38 (0.73–2.64)

Note: Bolded information denotes statistically significant different with $p < 0.05$. All models are stratified by cohorts.

Abbreviations: CI confidence interval; HR, hazard ratio; REF, reference.

[a]Models were adjusted for age, sex, pack-years of cigarette smoking, and alcohol consumption.

[b]Models were adjusted for age, pack-years of cigarette smoking, and alcohol consumption.

[c]Models were adjusted for age, sex and alcohol consumption.

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increasing age could be influenced by period or birth cohort effects. For example, studies conducted in Japan and China have reported differential mortality risks associated with cigarette smoking as a result of birth cohort-specific smoking patterns.[32,33] However, previous studies on the association between familial his and early-onset LC have yielded consistent results. Most studies, including a case–control study conducted in China[34] and a cohort study conducted in the United Kingdom,[35] reported higher familial risk of LC among younger participants. In a recent meta-analysis, younger individuals were associated with an increased familial LC risk, which is consistent with our results.[5]

Overall, there were no significant differences between the three Asian countries studied. However, further stratification by smoking status and type of relatives revealed some differences. In Korea, FHLC was significantly associated only with LC incidence among never-smokers. This highlights the importance of considering FHLC risk assessment among never-smokers in Korea. The effect of relative type differed across China, Japan, and Korea. These findings suggest genetic, environmental, cultural, and lifestyle differences may influence disease transmission and risk, indicating the importance of accounting for regional variations when using family history for LC screening.

This is a large pooled analysis of 11 prospective cohorts, including almost half a million participants with individual-level data, aimed at assessing the association between FHLC with the risk of LC incidence and mortality. Unlike case–control studies where individuals were selected based on the presence or absence of disease, our analysis included only prospective cohorts, and information on FHLC was collected before the onset of LC, therefore eliminating the possibility of recall bias. However, some limitations of the study warrant consideration. Firstly, despite having a large sample size, we were unable to further stratify by sex, country, and smoking status for the less common LC subtypes due to the very small number of cases in each stratum. Secondly, there are potential confounding factors, such as air pollution, that were not available and therefore, not included in the analysis. Information on passive smoking was only provided by a subset of the cohorts. However, we performed a sensitivity analysis using the five cohort studies (JPHC I, JPHC II, JACC, KNCC, Namwon) with information on passive smoking by additionally adjusting for passive smoking in the model, and the results were similar (Table S13). Familial risk has been suggested to be associated with both shared environmental and genetic factors.[36] Therefore, future studies should account for environmental variables such as air pollution and passive smoking. Further research is also warranted to explore the underlying mechanisms in terms of genetic factors. Finally, deaths from causes other than LC were significantly higher than deaths from LC, suggesting potential censoring bias in our study. To minimize the possibility of censoring bias from deaths due to causes other than LC, we conducted a sensitivity analysis using a competing risks regression model, treating deaths from other causes as competing risks, and the results remained similar. In our study, the loss-to-follow-up rate was 6.4%, which is well below the commonly accepted threshold of 10% that typically raises concerns about potential selection bias.[37] Therefore, the possibility of censoring bias is minimal.

5 | CONCLUSIONS

This is the largest pooled prospective study including approximately half a million people to examine the association between FHLC with risk of LC incidence and mortality, and stratification by LC histological subtypes in the Asian population. We found that family history was significantly associated with an increased risk of LC incidence and mortality, particularly lung adenocarcinoma, squamous cell carcinoma LC, and other non-small cell LC. The significant and positive associations were consistently observed across sex, smoking status, and country. Therefore, we suggest that family history can be used as a simple proxy for genetic risk that can be easily and inexpensively obtained. Future research is warranted to investigate the underlying mechanisms and various environmental exposures, such as air pollution, which is prevalent in Asia.

AUTHOR CONTRIBUTIONS

Rie Kishida: Conceptualization; formal analysis; methodology; writing—original draft; writing—review & editing. **Xin Yin:** Formal analysis; methodology; writing—review & editing. **Sarah Krull Abe:** Data curation; project administration. **Md. Shafiur Rahman:** Data curation; project administration. **Eiko Saito:** Data curation; project administration. **Md. Rashedul Islam:** Data curation; project administration. **Qing Lan:** Methodology; writing—review & editing. **Batel Blechter:** Methodology; writing—review & editing. **Nathaniel Rothman:** Methodology; writing—review & editing. **Norie Sawada:** Resources; writing—review & editing. **Akiko Tamakoshi:** Resources; writing—review & editing. **Xiao-Ou Shu:** Resources; writing—review & editing. **Atsushi Hozawa:** Resources; writing—review & editing. **Seiki Kanemura:** Resources; writing—review & editing. **Jeongseon Kim:** Resources; writing—review & editing. **Yumi Sugawara:** Resources; writing—review & editing. **Sue K. Park:** Resources; writing—review & editing. **Sun-Seog Kweon:** Resources; writing—review & editing. **Habibul Ahsan:** Resources; writing—review & editing. **Paolo Boffetta:** Resources; writing—review & editing. **Kee Seng Chia:** Resources; writing—review & editing. **Keitaro Matsuo:** Resources; writing—review & editing. **You-Lin Qiao:** Resources; writing—review & editing. **Wei Zheng:** Resources; writing—review & editing. **Manami Inoue:** Resources; writing—review & editing. **Daehee Kang:** Resources; writing—review & editing. **Wei Jie Seow:** Conceptualization; methodology; writing—review & editing; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data underlying the findings of our study are available from the corresponding author upon reasonable request and with permission from ACC.

ETHICS STATEMENT

The project was approved by the executive committee of the Asia Cohort Consortium and by the ethical committee of the National Cancer Centre Japan (number 2014-041, Tokyo, Japan). All cohorts have been approved by their respective institutional review boards and obtained informed consent from their participants based on their approved protocol.

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