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The clinical impact of family history of cancer in female never-smoker lung adenocarcinoma

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ABSTRACT

Objectives: Accumulating evidence reveals the association between the risk of never-smoker lung cancer and family history of cancer. However, the clinicogenomic effect of family history of cancer in never-smoker lung cancer remains unknown.

Material and methods: We screened 3,241 lung cancer patients who (a) underwent curative resection at National Cancer Center (Goyang, Korea) between 2001–2014, and (b) completed a pre-designed interview about family/smoking history at the time of diagnosis and identified 604 female never smoker lung adenocarcinoma. A positive family history of cancer [categorized as pulmonary cancer (FH-PC) or non-pulmonary cancer (FH-NPC)] was defined as a self-reported history of cancer in first-degree relatives. Survival data were followed up until January 2017. Multiplexed targeted next-generation sequencing was performed for genetic profiling.

Results: Of 604 patients, 29.1% (n = 176) had a FH, including 132 (21.9%) with FH-NPC and 44 (7.3%) with FH-PC. Patients with the FH-NPC had a higher proportion of young patients (≤45 years) than those without the FH-NPC (FH-NPC, FH-PC, and no FH; 13.6%, 2.3%, and 8.2%, respectively; $P = 0.032$). Patients with the FH-NPC had an increased risk of recurrence (hazard ratio [HR]: 1.90; 95% confidence interval [CI]: 1.40–2.56; $P < 0.001$) and death (HR: 1.67; 95% CI: 1.18–2.37; $P = 0.004$). In contrast, the FH-PC had no prognostic effect on recurrence (HR: 1.23; 95% CI: 0.71–2.15; $P = 0.456$) and death (HR: 0.93; 95% CI: 0.45–1.91; $P = 0.838$). Among three driver oncogene alterations, *EGFR* mutation was significantly associated with the FH-PC (53.8%, 84.1%, and 65.8%, respectively; $P = 0.016$), *ALK/ROS1/RET* fusions was significantly associated with the FH-NPC (13.7%, 0.0%, and 5.0%, respectively; $P = 0.004$), but *KRAS* mutation was not associated with any type of the FH (13.8% vs. 6.0% vs. 7.8%, respectively; $P = 0.288$).

Conclusion: The type of family history of cancer was associated with distinct clinocogenomic subtypes and prognosis of never-smoker lung adenocarcinoma.

1. Introduction

Lung cancer is a major cause of cancer death worldwide [1]. Most lung cancer are attributed to tobacco smoke but approximately 25% of lung cancers occur in lifelong never-smokers [1]. Moreover, the incidence of lung cancer in never-smokers has been increasing annually [2–4]. However, the definitive cause of lung cancer in never-smokers has not yet been identified. Many genetic, environmental, hormonal, and viral factors have been proposed as candidate risk factors of lung cancer in never-smokers. Accumulating evidence suggested the association between the risk of lung cancer in never-smokers and family history of cancer. A few population-based studies reported significant cancer aggregation in families of never-smokers with lung cancer [5–7]. A linkage analysis of 52 families found a major genetic susceptibility locus for inherited lung cancer on chromosome 6q23–25 [8]. More recently, some researchers reported that a family with multiple members who developed lung cancer was associated with the germline *EGFR* T790 M mutation, or with the germline *EGFR* V843I mutation, which is a secondary somatic mutation linked to resistance to EGFR tyrosine kinase inhibitors (TKIs) [9,10]. These findings provide insights into the importance of inherited genetic factors in driving lung cancer in never-smokers.

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Recent studies have also suggested that a family history of cancer is associated with prognosis in several cancer types. A family history of colorectal cancer was significantly associated with better prognosis in colorectal cancer patients [11,12]. In addition to, breast cancer patients with a family history of breast or ovarian cancer showed longer survival than those without them [13]. There are conflicting data in patients with gastric cancer. A Korean study demonstrated that a family history of gastric cancer was associated with better prognosis after curative resection of gastric cancer [14]. By contrast, a different study reported that patients with a family history of gastric cancer showed a significant increase in cancer recurrence or death [15]. Among studies of lung cancer, a retrospective study evaluating 560 patients with stage I–IV non-small cell lung cancer (NSCLC) showed that a family history of lung cancer was associated with worse prognosis [16]. By contrast, other studies have showed that a family history of lung cancer was associated with higher likelihood of *EGFR* mutations and longer survival in NSCLC patients [17,18]. These conflicting results may originate from differences in study populations including sex, smoking status, histology, stage, and treatment. Therefore, this study evaluated the clinicogenomic features and prognostic impact of family history of cancer in patients with lung cancer in a more homogenous patient population of female never-smokers with early-stage lung adenocarcinoma (NSLA).

2. Methods

2.1. Patients and sample collection

We reviewed medical records of 3,241 consecutive patients who underwent curative resection of lung cancer at the National Cancer Center (Goyang, Korea) between January 2001–January 2014 and were enrolled into the National Cancer Center Lung Cancer Surgery Registry (Supplement Fig. 1). 2940 patients (90.7%) who completed pre-designed self-reporting interview questions about their family histories of cancer, past illness, and smoking history at the time of diagnosis, were potentially eligible for this study. Our study cohort included patients who (1) were ≥18 years of age, (2) were female, (3) had no smoking history, (4) had pathological stage I–III tumors, (5) had tumors with adenocarcinoma histology, (6) received no neoadjuvant treatment, and (7) had available tumor tissue for targeted sequencing. 'Never-smoker' was defined as a patient who had smoked < 100 cigarettes in her life. A positive family history of cancer (FH) was defined as a self-reported history of cancer in first-degree relatives (parent, sibling, or offspring with cancer) and was classified into two cancer types [pulmonary cancer (FH-PC) and non-pulmonary cancer (FH-NPC)]. If the patients had family history of both lung cancer and other cancers, they were regarded as having FH-PC. This study was approved by the Institutional Review of Board of the National Cancer Center (Goyang, Korea; protocol number: NCC 2017-0076).

2.2. Treatment and follow-up

Pre-operative evaluation was performed by administering a pulmonary function test, chest computed tomography (CT), positron emission tomography scan, flexible bronchoscopy with or without endobronchial ultrasound bronchoscopy procedure, and brain magnetic resonance to all patients in the study. Standard surgical procedures of anatomic lung resection and systematic lymph node dissection were performed on all patients in the study cohort. Postoperative evaluation was carried out via a physical examination, chest x-ray, and chest CT. Postoperative surveillance was performed every 3 months during the first 2 years, every 6 months from the second to the fifth year, and annually thereafter. Recurrence was determined by the presence of radiologic findings or histologic confirmation. Most patients with stage II–III cancer received adjuvant chemotherapy with platinum-based doublet regimen (navelbine or paclitaxel) every 3 weeks for four cycles.

2.3. Histological evaluation

A lung cancer pathologist (G. K. L.) confirmed the histology of adenocarcinoma and tumor cell content within each tumor sample used for targeted sequencing. Tissues with > 20% tumor cells in hematoxylin-and-eosin-stained sections were subjected to targeted sequencing assay.

2.4. Targeted next-generation sequencing (NGS) assay

For comprehensive genomic analysis, several driver oncogenes were simultaneously profiled via multiplex targeted NGS. Targeted NGS was performed in 430 tumors which were wild-type or unknown status for *EGFR*, *ALK*, and *KRAS* mutations. The DNA from formalin-fixed paraffin-embedded (FFPE) tumor tissues was extracted with the QIAamp DNA FFPE Tissue Kit (Qiagen, Valencia, CA), according to the manufacturer's instructions. DNA libraries were prepared with Axen Cancer Panel 1, and developed by Macrogen (Macrogen, Seoul, Korea), which covers the exons of 88 cancer-related genes and the introns of three genes frequently rearranged in lung cancer (Supplement Table 1). The DNA libraries were paired-end sequenced (2 × 150 bp) with a NextSeq 500 instrument (Illumina, San Diego, CA) with high output, using sequencing by synthesis chemistry to a depth of 2000× the average coverage.

2.5. Conventional gene mutation test

We identified 174 patients with tumors harboring *EGFR, ALK,* or *KRAS* mutations by conventional gene mutation tests at the time of diagnosis. An additional targeted sequencing test was not performed in these patients. The peptide nucleic acid (PNA)-mediated real-time PCR clamping method or direct sequencing were used to sequence the *EGFR* gene (exons 18, 19, 20, and 21). Direct sequencing was used for the *KRAS* gene (exons 12 and 13), and fluorescence *in situ* hybridization was used to detect any *ALK* gene rearrangement.

2.6. Statistical analysis

Pearson's χ^2 test or Fisher's exact test were used to determine relationships between categorical variables, where appropriate. Recurrence-free survival (RFS) was calculated from the date of surgical resection and the date of radiological or pathological documentation of recurrence, death with recurrence, or occurrence of a new primary lung cancer. Overall survival (OS) was calculated from the date of surgical resection until the date of death or the most recent follow-up. Survival time was estimated with the Kaplan-Meier method, and the difference in survival between groups was assessed via a log-rank test. Cox proportional hazards models were used for the multivariate analyses of survival. Two-sided *P*-values < 0.05 were considered significant.

3. Results

3.1. Family history

Of 3,241 early-stage lung cancer patients, 604 female NSLA were eligible for inclusion into our study cohort (Supplement Fig. 1). The median age of the patients was 60 years (range, 28–85 years) and the proportion of stage I tumors was 68.4%. Of these patients, 29.1% (n = 176) of patients had a family history of cancer in first-degree relatives (Table 1). By cancer type, 21.9% (n = 132) had FH-NPC and 7.3% (n = 44) had FH-PC.

3.2. Clinicopathologic features

The clinicopathologic characteristics of patients are shown in Table 2. Patients with FH-NPC were younger than those with FH-PC and

Table 1
Family history of cancer.

Type	No. of Patients (%)
Any cancer	
No	428 (70.9)
Yes	176 (29.1)
No of relatives of cancer	
1	132 (21.8)
≥2	44 (7.3)
Type	
Pulmonary cancer	44 (7.3)
Non-pulmonary cancer	132 (21.8≥21.9)
Non-pulmonary cancer	
No	472 (78.1)
Yes	132 (21.8)
No of relatives of cancer	
1	103 (17.0)
≥ 2	29 (4.8)
Type	
Gastric cancer	44 (7.3)
Liver cancer	31 (5.1)
Colorectal cancer	18 (2.9)
Pancreatic cancer	14 (2.4)
Breast cancer	10 (1.7)
Pulmonary cancer	
No	560 (92.7)
Yes	44 (7.3)
No of relatives of cancer	
1	29 (4.8)
≥ 2	15 (2.5)

those without FH (median age; 59 years vs. 60years vs. 61 years; $P = 0.050$). The proportion of young patients (≤45 years) was 13 of 132 (13.6%) among patients with FH-NPC whereas it was 1 of 44 (2.3%) in those with FH-PC and 36 of 472 (6.0%) in those without FH ($P = 0.032$). There was no difference in past illness, pathologic stage, operation method, and postoperative treatment among three subgroups by the FH type.

3.3. Prognostic impact

Survival data were followed up until January 2017 and the median follow-up period was 84.7 months (95% confidence interval [CI]: 77.8–91.6 months). At the time of analysis, 212 (35.1%) patients had experienced postoperative recurrence and 169 patients (28.0%) had died. The 5-year RFS rates for NSLA stages IA, IB, IIA, IIB, and IIIA were 90.5%, 76.0%, 51.7%, 33.4%, and 29.3%, respectively, and the 5-year OS rates were 93.7%, 88.4%, 72.4%, 51.2%, and 47.2% respectively.

In a univariate analysis of survival, the FH-NPC had an increased risk of recurrence ($P = 0.004$) or death ($P = 0.060$) compared with those without FH (Supplement Table 2). By contrast, the FH-PC had no difference in the risk of recurrence ($P = 0.977$) or death ($P = 0.397$) in comparison to those without FH. Multivariate analysis using age, stage, and adjuvant chemotherapy as covariates showed a significant association between the risk of recurrence or death and FH-NPC in first-degree relatives. The risk of recurrence after curative resection was significantly higher in those patients with FH-NPC than those without FH (hazard ratio [HR]: 1.90; 95% CI: 1.40–2.56; $P < 0.001$). Moreover, the patients with FH-NPC had the higher risk of death after curative resection compared those without FH (HR: 1.67; 95% CI: 1.18–2.37; $P = 0.004$). Thus, the median RFS and OS were significantly shorter in patients with FH-NPC compared to those without FH-NPC (Fig. 1). These results were consistent through the subgroup analyses that divided the patients based on pathological stage (stage I and stage II–III) except in the OS analysis of patients with stage I disease (Fig. 1).

3.4. Genomic features

We evaluated genomic features based upon family history of cancer in 430 patients whose tumor samples were subjected to multiplexed targeted NGS. In a total of 430 patients with early-stage NSLA, 323 patients (75.1%) carried at least one of seven driver oncogenic changes and the frequencies of changes in the common oncogenes, *EGFR*, *KRAS*, and *ALK* were 65.6%, 8.3%, and 4.3%, respectively (Fig. 2A). Among the three FH groups, there was no difference in the rank of driver oncogenes but a significant difference in the specific frequency of each gene. In the FH-NPC group, *EGFR*, *KRAS*, and *ALK* were 53.8%, 13.8%, and 10.6%, respectively (Fig. 2B). In the FH-PC group, *EGFR and KRAS* were 84.1% and 6.0%, respectively (Fig. 2C). *EGFR* mutations were less frequent in patients with FH-NPC compared to those with FH-PC and those without FH (53.8% vs. 84.1% vs. 65.8%, respectively; $P = 0.016$) (Fig. 3A). By contrast, *ALK* rearrangement was more frequent in patients with FH-NPC compared to those with FH-PC and those without FH (10.6% vs. 0.0% vs. 4.1%, respectively; $P = 0.028$) (Fig. 3B). The frequency of rearrangements in three genes including *ALK, ROS1,* and *RET* was significantly higher in patients with FH-NPC compared to those with FH-PC and those without FH (13.7% vs. 0.0% vs. 5.0%, respectively; $P = 0.004$) (Fig. 3B). There was no difference in the frequency of *KRAS* mutations among patients with FH-NPC, patients with FH-PC, and those without FH (13.8% vs. 6.0% vs. 7.8%, respectively; $P = 0.288$) (Fig. 3C). Among cancer susceptibility genes, *CDH1* mutation was more frequent in patients with FH-NPC compared to those with FH-PC and those without FH (14% vs. 6% vs. 6%, respectively;

Table 2
Patient characteristics.

Characteristics	Category	FH-NPC (N = 132) No (%)	FH-PC (N = 44) No. (%)	No FH (N = 428) No. (%)	P*
Age, years	Median	59	60	61	0.050†
	≤45	18 (13.6)	1 (2.3)	35 (8.2)	0.032
	> 45	114 (86.4)	43 (97.7)	393 (91.8)	
Past illness	Yes	10 (7.6)	0 (0.0)	32 (7.5)	0.751
Pathological stage‡	IA	46 (34.8)	14 (31.8)	126 (29.4)	0.503
	IB	39 (29.5)	20 (45.5)	139 (32.5)	
	IIA	11 (8.3)	2 (4.5)	60 (14.0)	
	IIB	7 (5.3)	3 (6.8)	15 (3.5)	
	IIIA	29 (22.0)	5 (11.4)	88 (20.6)	
Surgery method	Lobectomy	98 (74.2)	29 (65.9)	280 (65.4)	0.411
	Pneumonectomy	8 (6.0)	4 (9.1)	44 (10.3)	
	Others	26 (19.7)	11 (25.0)	104 (24.3)	
Adjuvant chemotherapy	Yes	38 (28.8)	8 (18.2)	130 (30.4)	0.237
Adjuvant radiotherapy	Yes	2 (1.5)	1 (2.3)	9 (2.1)	0.506

Notes: * tested with Pearson's χ^2 test or Fisher's exact test; †tested with Mann-Whitney test; ‡staging according to the 7th edition of the American Joint Commission on Cancer Staging System. Abbreviations: FH-NPC; family history of nonpulmonary cancer; FH-PC, family history of pulmonary cancer; FH, family history of cancer.

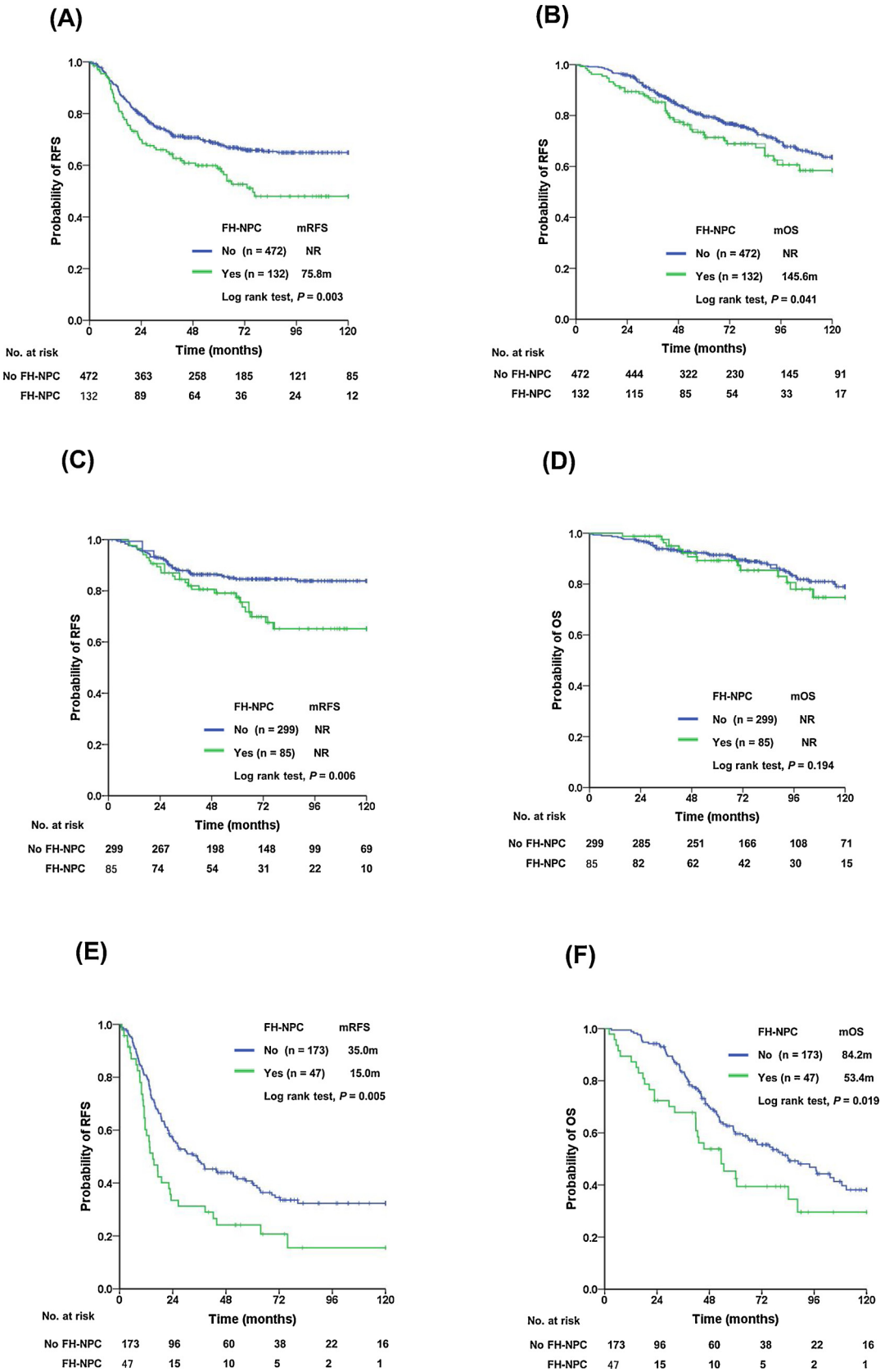

Fig. 1. Kaplan-Meier survival curves of study cohort patients stratified by presence/absence of a family history of non-pulmonary cancer. (A) RFS, (B) OS, in patients with disease stage I–III; (C) RFS, (D) OS, in patients with stage I disease; (E) RFS, (F) OS, in patients with stage II–III disease. Abbreviations: RFS, recurrence-free survival; OS, overall survival; FH-NPC, family history of non-pulmonary cancer; NR, not reached; mRFS, median recurrence free survival mOS, median overall survival.

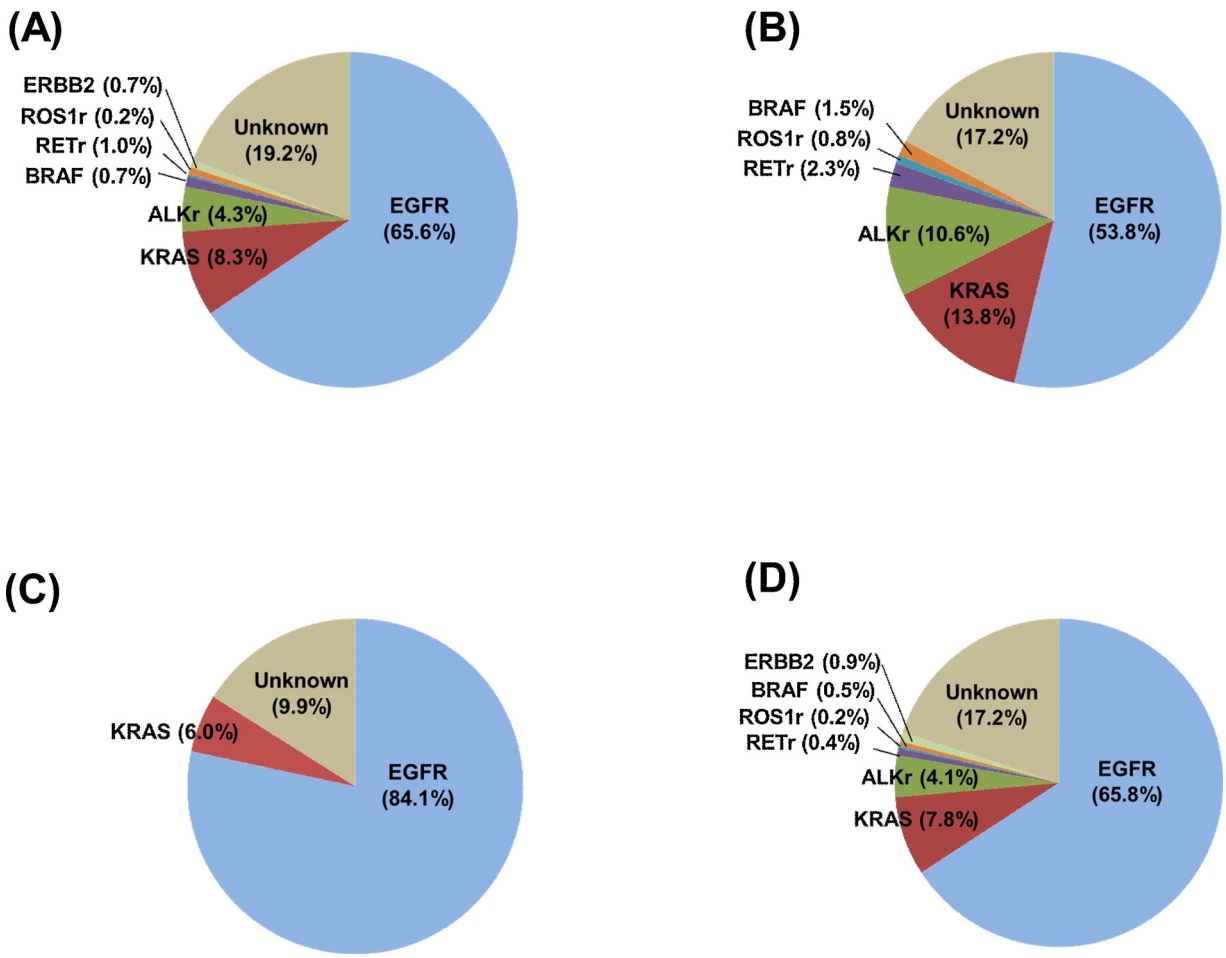

Fig. 2. Frequencies of driver gene alterations. (A) In total patients (n = 430), (B) in patients with family history of non-pulmonary cancer (n = 85), (C) in patients with family history of pulmonary cancer (n = 32), and (D) in patients with no family history of cancer (n = 313), driver gene alterations was ranked. Abbreviations: ALKr, ALK rearrangement; ROS1r, ROS1 rearrangement; RETr, RET rearrangement.

$P = 0.070$), even though there was no statistical significance (Fig. 4).

Among *EGFR, ALK,* and *KRAS* gene alterations, *EGFR* mutations only showed a significant association with survival outcomes in early-stage NSLA patients (Supplement Table 3). In multivariate analysis adjusting for stage and FH-NPC, the *EGFR*-mutant tumors showed the reduced risk of recurrence (HR, 0.72; 95% CI, 0.53–0.97; $P = 0.030$) and death (HR, 0.73; 95% CI, 0.53–0.98; $P = 0.040$) compared with the *EGFR*-wild type tumors.

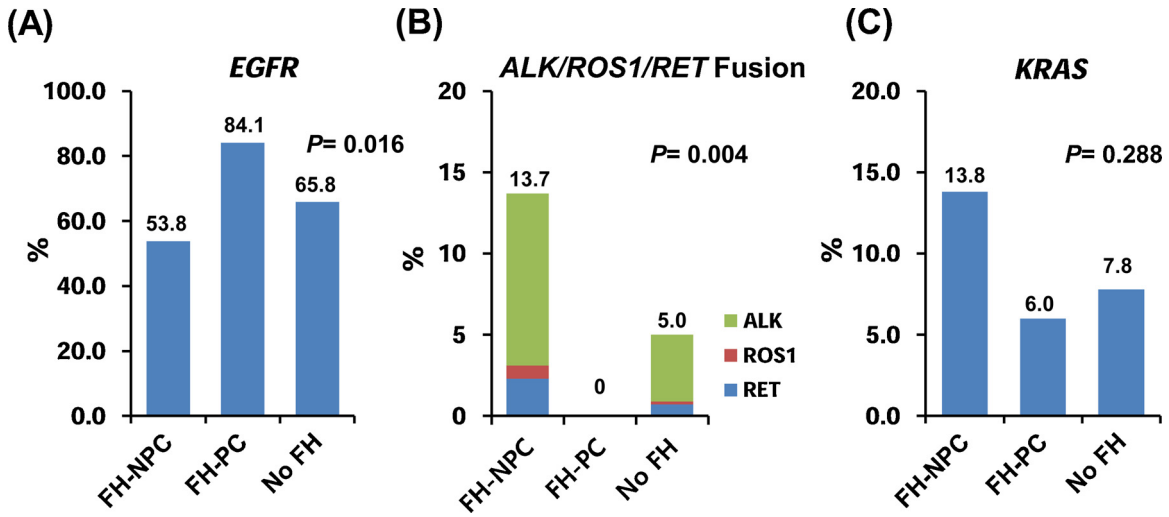

Fig. 3. Frequencies of genetic alterations according to the family history of cancer. The frequency of (A) *EGFR* mutations, (B) *ALK, ROS1,* and *RET* fusion, and (C) *KRAS* mutations were compared by the type of family history of cancer. Abbreviations: FH-NPC, family history of non-pulmonary cancer; FH-PC, family history of pulmonary cancer; FH, family history of any cancer. Note: The test with Pearson's χ^2 test or Fisher's exact test was used.

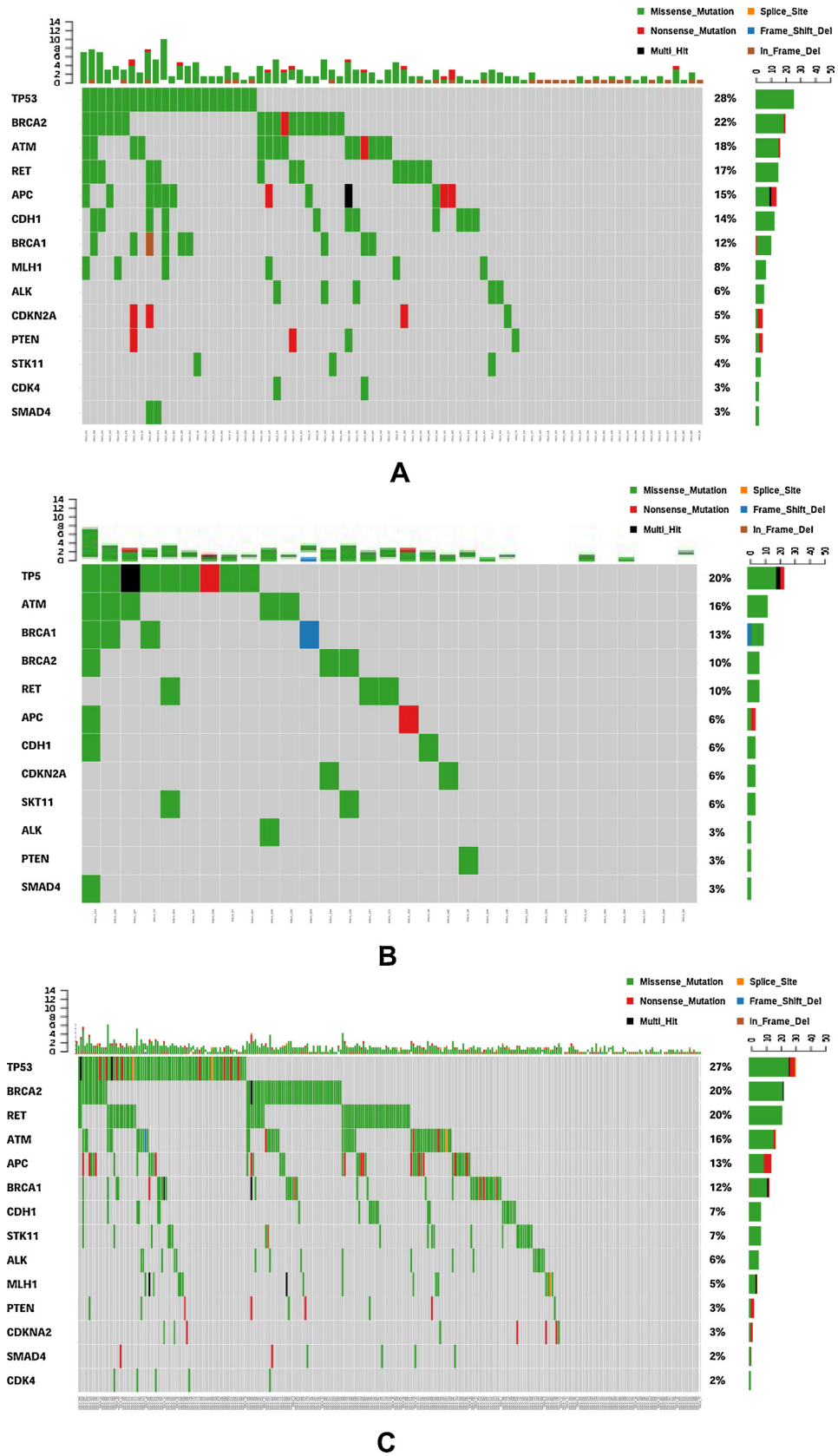

Fig. 4. Oncoprint depicting the frequencies of genetic alterations in cancer susceptibility genes (A) in patients with family history of non-pulmonary cancer (n = 85), (B) in patients with family history of pulmonary cancer (n = 32), and (C) in patients with no family history of cancer (n = 313).

The multivariate analysis including stage, *EGFR* mutations, and FH-NPC demonstrated that significant association between FH-NPC and survival (HR for recurrence, 1.86; 95% CI, 1.38–2.52; $P < 0.001$; HR for death, 1.66; 95% CI, 1.18–2.35; $P = 0.004$) (Supplement Table 4). In the subgroup with *EGFR* mutations, FH-NPC was associated with the increased risk of recurrence (HR, 1.66; 95% CI, 1.12–2.47; $P = 0.012$) and death (HR, 1.34; 95% CI, 0.82–1.09; $P = 0.051$) (Supplement Table 5).

4. Discussion

This study comprehensively investigated the clinicogenomic effect of family history of cancer in 604 female Korean never smokers with early-stage lung adenocarcinoma. Among 604 NSLA in our cohort, 132 (21.9%) had FH-NPC and 44 (7.3%) had FH-PC. The FH-PC was significantly related to higher frequency of *EGFR* mutations but had no prognostic effect in NSLA. On the other hand, the FH-NPC was significantly associated with younger age and presence of *ALK/ROS1/RET* gene fusions. Importantly, a FH-NPC significantly increased the risk of recurrence and death in NSLA, independently of known prognostic factors. Most previous studies reporting a relationship between a family history of cancer and risk of lung cancer have focused on FH-PC rather than on FH-NPC [7,8]. However, we reported firstly the clinicogenomic and prognostic effect of FH-NPC in patients with lung cancer.

Interestingly, this study showed the frequency of driver oncogene alterations was different according to the type of FH. The frequency of *EGFR* mutations was significantly higher in patients with FH-PC, which was consistent with the findings from other studies [19,20]. Meanwhile, the frequency of *ALK/ROS1/RET* fusions was significantly higher in patients with the FH-NPC. However, the frequency of *KRAS* mutations was so even regardless of the type of FH. This finding suggests the pathogenesis of each oncogene-addictive tumor type seems to be quite different, even though these tumor types occur in never smokers.

Studies have previously reported associations between a family history of cancer and prognosis in lung cancer [16–18,20]. In a Chinese study including 4,491 patients with stage I–IV NSCLC diagnosed between 1999–2005, the frequencies of females, non-smokers, young age, and adenocarcinoma histology were higher in the subgroup of patients with a family history of cancer than in the subgroup without [17]. The study concluded that family history of any cancer had no prognostic effect, but a family history of lung cancer was associated with better prognosis in both early and advanced-stage NSCLC. A Spanish epidemiologic study focusing on female patients with lung cancer diagnosed between 2007–2012 suggested significant associations between a family history of cancer or lung cancer and a favorable prognosis [18]. On the other hand, Ganti et al. who analyzed 560 lung cancer patients (51% of whom were males and 93% of whom were smokers) reported that a positive FH-PC increased the risk of death [16]. A Korean study including 829 NSCLC patients diagnosed between 2006–2014 showed that *EGFR* mutations were more commonly detected in patients with a FH-PC and found no association between FH-PC and prognosis [20]. The results of that study were consistent with those of our study. The discrepancy among these studies may be attributed to heterogeneous patient characteristics. Patient cohorts in all the afore-mentioned studies included 40–60% of patients with stage IV disease; thus, the survival of these advanced-stage patients had a significant effect on OS of the study cohort. *EGFR* TKIs have showed a significant survival benefit in patients whose tumors harbor *EGFR* mutations and have therefore been routinely used in clinical practice after the mid-2000s [21–24]. Thus, we should consider the survival effect of EGFR-TKI treatment in interpreting survival data of patients with lung cancer in never smokers. In the Spanish study including female patients who were diagnosed after the mid-2000s, patients with FH-PC likely received a significant survival benefit from EGFR TKIs compared to patients without FH-PC while those with FH-PC would not in the Ganti et al. study which mostly included patients who were smokers diagnosed before the mid-2000s. In our study, FH-PC had no prognostic effect in terms of recurrence and death. Although our study included NSLA patients diagnosed after the mid-2000s, the effect of EGFR TKIs on survival seems to be insignificant because of high proportion of stage I tumor (68.4%).

In contrast to FH-PC, FH-NPC was significantly associated with worse prognosis in this study. In addition to, patients with FH-NPC were more likely to harbor fusion gene including *ALK* rearrangement. Several studies reported *ALK* rearrangement is common in young-age onset lung cancer and associated with unfavorable prognosis for lung adenocarcinoma [25–27]. Poor prognosis of patients with FH-NPC seems to be in keeping with these previous reports. We examined whether the patients with FH-NPC had worse prognosis because they had fewer *EGFR*-mutant tumors with better prognosis. A FH-NPC was found to be an independent prognostic factor for recurrence and death in our multivariate survival analysis that included the *EGFR* mutation status of their tumors. Even in the subgroup with *EGFR*-mutant tumors, patients with FH-NPC showed an increased risk of recurrence and death than those without. However, it is currently unclear why a FH-NPC adversely affects survival in NSLA. A family history of cancer may affect cancer survival in terms of health-related behavior, adherence to cancer surveillance, and shared environmental and genetic differences. There seems to be little difference in health-related behavior because our study's subjects were restricted to females with no smoking history. Moreover, the difference in adherence to cancer surveillance was less likely to drive differences in survival of these NSLA. Individuals with family history of cancer are more likely to receive cancer screening and thus to have earlier tumor stage and improved survival than those without, in contrast to our findings [28,29]. The most convincing explanation of the observed association between FH-NPC and survival may be genetic differences. In this relatively homogenous study population, young-age onset, distinct gene alteration pattern, and familial aggregation suggest the existence of inherited genetic components. The prognostic effect of a FH-NPC may arise from germline genetic alterations that aggravate cancer progression or metastasis. This potential gene alteration may be present together with fusion genes but be perhaps mutually exclusive with *EGFR* mutations, and be related to women's cancer susceptibility genes. Of cancer susceptibility gene, the frequency of *CDH1* mutation was numerically higher in patients with FH-NPC than others without statistical significance. Recently, Cho et al. reported somatic *CDH1* mutation is common (42.2%) in early-onset diffuse gastric cancer which has usually aggressive clinical course and occurs more frequently in women [30]. Further more comprehensive genetic studies are needed to discover and validate causable genetic factors including *CDH1* mutation.

Although our study has offered extremely valuable insights, it does have a few notable limitations. First, this study was based on self-reported family history. Although we included a family history of cancer only in first-degree relatives (and not in second- or third-degree relatives), we could not systematically avoid recall bias. Second, this study did not have detailed information about cancer screening or lifestyle habits including second-hand smoking, which could shed light on why there is a significant difference in prognosis between NSLA patients with and without a FH-NPC. Third, germline mutation tests to identify hereditary cancer syndrome were not performed. Our findings potentially implicate genetic components with a hereditary nature in NSLA patients with a FH-NPC. Thus, it is necessary to evaluate gene alterations related to hereditary cancer syndrome in this patient population.

5. Conclusion

The clinical and genomic features of lung cancer in never smokers may be different according to the type of family caner history. The frequency of *ALK/ROS1/RET* fusions is higher in the patients with FH-NPC while the frequency of *EGFR* mutation is higher in the patients with FH-PC. A FH-NPC may be associated with early-onset tumor and

worse prognosis in never smoker lung cancer. More active surveillance for postoperative recurrence and mutation profiles specific to the type of FH might be required for this high-risk population. Moreover, early incorporation of molecular-targeted agents into adjuvant treatment setting warrants consideration for these patients.

Declaration of Competing Interest

The authors indicated no potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.07.031.

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