Letter to the Editor

Impact of family history of cancer on development of lung cancer among the Korean population: a prospective cohort study using KoGES data

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Several studies have indicated a potential link between a family history of cancer, particularly lung cancer, and an increased risk of developing lung cancer (1-3). However, the impact of a history of specific types of cancer on lung cancer risk remains uncertain (4). Confirming this association is crucial to improve the accuracy of lung cancer prediction and to identify groups at high risk to enable timely lung cancer screening (5). Hence, this study aimed to investigate the connection between a family history of cancer in first-degree relatives (FDRs) and the risk of lung cancer in the Korean population by assessing the family history of cancer (lung cancer and others) in individuals with and without lung cancer.

We used cohort data from the Korean Genome and Epidemiology Study (KoGES). Detailed information was reported in a previous study (6,7). Of a total of 211,562 individuals, we excluded 10,030 without data regarding a family history of cancer and 1,672 with missing values in smoking status. Of the remaining, 68,632 individuals aged younger than 50 years were further excluded. Finally, 131,228 individuals were included in the final analyses.

Family history of cancers in FDRs and the presence of lung cancer were assessed using questionnaires. A recent study suggested that a family history of lung cancer may have a more pronounced influence on the risk of lung cancer than a family history of other types of cancers (4). Given this evidence, we placed greater emphasis on investigating the impact of a family history of lung cancer. We classified the family history of FDRs into two categories: lung cancer and cancers other than lung cancer (hereafter referred to as other cancers). We also evaluated the risk of lung cancer based on the number of FDRs with a history of cancer (single *vs.* multiple) to explore potential associations between the number of affected relatives and the risk of developing lung cancer. Furthermore, considering smoking as a well-established risk factor for lung cancer, we performed subgroup analysis for sex and smoking status to determine potential genetic susceptibility factors that may contribute to the development of lung cancer in the absence of smoking-related factors.

Multivariable logistic analysis was performed to

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determine the association between a family history of cancer and the development of lung cancer. Age, sex, and smoking status (current, former, and never) were used as covariates. However, in the subgroup analysis, it was not possible to adjust for sex in the ever-smoker subgroup and smoking status in the female subgroup due to the limited number of lung cancer cases. All analyses were performed using R version 4.1.3 (R core Team 2020; R Foundation for Statistical Computing, Vienna, Austria).

Of 131,228 individuals, the numbers of individuals with a family history of cancers were as follows: (I) 4,555 (3.5%) individuals with a family history of lung cancer; (II) 23,155 (17.6%) individuals with a family history of other cancers; (III) 24,471 (18.6%) individuals with a family history of single cancer; and (IV) 3,239 (2.5%) individuals with a family history of multiple cancers. Out of the total, there were 135 (0.1%) cases of lung cancer, distributed as 9 (0.2%) out of 4,555 in those with a family history of lung cancer, 32 (0.1%) out of 23,155 in those with a family history of other cancers, 34 (0.1%) out of 24,471 in those with a family history of single cancer, and 7 (0.2%) out of 3,239 in those with a family history of multiple cancers. Among individuals without any family history of cancer, there were 94 (0.1%) cases of lung cancer out of 103,424.

As shown in *Table 1*, a family history of lung cancer significantly increased the risk of lung cancer [adjusted odds ratio (aOR) =2.51, 95% confidence interval (CI): 1.26–4.99]. A family history of other cancers was also associated with an increased risk of lung cancer (aOR =1.74, 95% CI: 1.16–2.60). Additionally, regardless of the number of FDRs with a family history of cancer, a family history of cancer increased the risk of lung cancer. Although not statistically significant, the odds of developing lung cancer were approximately 1.7 (95% CI: 0.74–3.78) times higher for individuals with a family history of multiple cancers (aOR =2.90, 95% CI: 1.34–6.28) than those with a family history of single cancer (aOR =1.74, 95% CI: 1.17–2.58).

In subgroup analysis, family histories of lung cancer and multiple cancers were associated with an increased risk of lung cancer among females and never-smokers. Specifically, in females, the odds of developing lung cancer were significantly higher for those with a family history of lung cancer (aOR =4.44, 95% CI: 1.85–10.68), and the same was true for multiple cancers (aOR =3.87, 95% CI: 1.36–11.00). Among never-smokers, the risk of developing lung cancer was significantly elevated for individuals with a family history of lung cancer (aOR =3.77, 95% CI: 1.59–8.93) and multiple cancers (aOR =3.37, 95% CI: 1.20–9.47). However, in ever-smokers, family histories of other cancers and single cancers were associated with an increased risk of lung cancer (aOR =2.21, 95% CI: 1.33–3.67 for other cancers; aOR =2.04, 95% CI: 1.23–3.40 for single cancers). Among males, only family histories of lung cancer and single cancer were associated with a significantly increased risk of lung cancer (aOR =1.92, 95% CI: 1.18–3.14 for lung cancer; aOR =1.79, 95% CI: 1.10–2.92).

Our study findings support previous research (1,4) by confirming that a family history of lung cancer is associated with an elevated risk of developing lung cancer. Moreover, we observed that a family history of cancers other than lung cancers also increased the likelihood of developing lung cancer. Irrespective of the number of affected relatives, a family history of cancer in FDRs contributed to an increased risk of lung cancer, with a greater impact in cases with multiple cancers. These results emphasize the need for personalized approaches to lung cancer screening rather than relying solely on a single criterion. To ensure early detection of lung cancer through precision medicine, it is crucial to conduct a comprehensive evaluation of a patient's family history of cancer in FDRs, along with considering other relevant clinical factors (8). This approach will help guide the decision-making process for lung cancer screening.

The impact of a family history of cancer in FDR on the risk of lung cancer varies by subgroup. Particularly, the role of family history of lung cancer appears to be less prominent among ever-smokers, indicating that smoking plays a more dominant role in the development of lung cancer in this population than do genetic factors. However, in other subgroups, such as females or never-smokers, a family history of lung cancer was consistently correlated with an increased risk of lung cancer. Therefore, it is imperative to conduct further research to evaluate the effectiveness of lung cancer screening, specifically in those individuals without a smoking history but with a family history of lung cancer in FDRs.

The limitation of this study is that the number of individuals with lung cancer was too small to draw definitive conclusions. Thus, future studies involving a larger number of participants are necessary to validate and strengthen our findings. Moreover, important characteristics of lung cancer, such as its pathology and types like primary, recurrent, and metastatic lung cancer, could not be assessed due to the lack of available data.

In conclusion, our study suggests that the development of lung cancer is associated with a family history of cancers, particularly lung cancer and multiple cancers.

Table 1 Odds ratios for risk of lung cancer by family history of any cancer

Family history of cancer in FDRs	Risk of lung cancer					
	Unadjusted			Adjusted		
	OR	95% CI	P value	OR	95% CI	P value
Total population (n=131,228)						
No family history of cancer	Ref.	Ref.		Ref.	Ref.	
Lung cancer	2.18	1.10–4.32	0.026*	2.51	1.26–4.99	0.007*
Cancer other than lung cancer	1.55	1.02–2.27	0.040*	1.74	1.16–2.60	0.009*
Single, any	1.53	1.03–2.27	0.034*	1.74	1.17–2.58	0.006*
Multiple, any	2.38	1.10–5.14	0.027*	2.90	1.34–6.28	0.007*
Gender						
Female (n=83,478)						
Lung cancer	4.18	1.74–10.03	0.001*	4.44	1.85–10.68	<0.001*
Cancer other than lung cancer	1.35	0.66–2.76	0.408	1.43	0.70–2.92	0.329
Single, any	1.55	0.80–3.02	0.197	1.64	0.84–3.20	0.148
Multiple, any	3.65	1.29–10.34	0.015*	3.87	1.36–11.00	0.011*
Male (n=47,750)						
Lung cancer	1.76	1.09–2.87	0.022*	1.92	1.18–3.14	0.009*
Cancer other than lung cancer	1.19	0.37–3.80	0.768	1.34	0.42–4.28	0.622
Single, any	1.63	1.01–2.66	0.048*	1.79	1.10–2.92	0.020*
Multiple, any	1.96	0.62–6.26	0.255	2.17	0.68–6.96	0.192
Smoking history						
Never-smoker (n=94,669)						
Lung cancer	3.48	1.47–8.22	0.005*	3.77	1.59–8.93	0.003*
Cancer other than lung cancer	1.22	0.63–2.39	0.553	1.31	0.67–2.57	0.426
Single, any	1.38	0.74–2.59	0.313	1.48	0.79–2.78	0.222
Multiple, any	3.09	1.10–8.66	0.032*	3.37	1.20–9.47	0.021*
Ever-smoker (n=36,559)						
Lung cancer	1.26	0.39–4.04	0.695	1.56	0.49–5.01	0.455
Cancer other than lung cancer	1.85	1.12–3.06	0.017*	2.21	1.33–3.67	0.002*
Single, any	1.71	1.03–2.83	0.037*	2.04	1.23–3.40	0.006*
Multiple, any	2.07	0.65–6.63	0.221	2.60	0.81–8.36	0.109

*, indicates statistical significance. FDRs, first-degree relatives; OR, odds ratio; CI, confidence interval.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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