

Association between humidifier disinfectant use duration and lung cancer development in Korea

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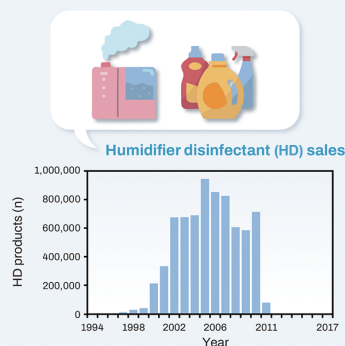
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Graphical Abstract

Association between humidifier disinfectant use duration and lung cancer development in Korea



Objectives



To evaluate the association between the duration of HD use and lung cancer development

Methods



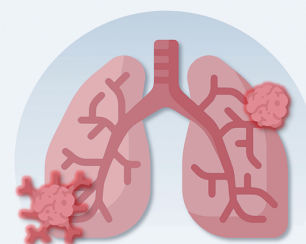
Data:

- 1) Survey for victims of HD exposure
- 2) Medical records from consented lung cancer patients

Statistical Analysis:

Survival analysis using Cox proportional hazard regression

Results



Compared to the duration of HD use less than 5 months, the risk of lung cancer in the group HD used for more than 5-14 months was 1.81 times, 2.45 times for 15-29 month, and 4.61 times for 30 months and more.

Conclusions

Prolonged HD use was associated with an increased risk of lung cancer development in a dose-dependent manner.

Key Message:

- There is a quantitative association between prolonged humidifier disinfectants use and the risk of lung cancer incidence.
- Individuals reported they used humidifier disinfectants for more than 30 months had more than four times higher risk of lung cancer than those of individuals who reported they used humidifier disinfectants for less than five months.

ORIGINAL ARTICLE

Association between humidifier disinfectant use duration and lung cancer development in Korea

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OBJECTIVES: This study was conducted to assess the association between the duration of humidifier disinfectant use and lung cancer development.

METHODS: We analyzed data from 3,605 applicants registered for compensation from the Korean government due to health conditions related to humidifier disinfectant exposure. Among these individuals, 121 were diagnosed with lung cancer at least 4 years after their initial exposure (through December 2021). Hazard ratios (HRs) and 95% confidence intervals (CIs) for lung cancer incidence were estimated according to the duration of disinfectant use using Cox proportional hazards models.

RESULTS: Compared with < 5 months of use, the HRs for lung cancer were 1.81 (95% CI, 0.41 to 7.97) for 5-14 months, 2.45 (95% CI, 0.58 to 10.41) for 15-29 months, and 4.61 (95% CI, 1.12 to 18.91) for ≥ 30 months. Using never smokers with < 15 months of use as the reference category, the HRs were 2.97 (95% CI, 1.34 to 6.56) for never smokers with ≥ 15 months of use, 2.73 (95% CI, 0.94 to 7.95) for current or former smokers with < 15 months of use, and 4.74 (95% CI, 1.94 to 11.61) for current or former smokers with ≥ 15 months of use.

CONCLUSIONS: Our study provides some of the first robust epidemiological evidence that prolonged humidifier disinfectant use contributes to lung cancer development. Future studies—particularly those including unexposed populations—are needed to confirm these findings.

KEY WORDS: Lung neoplasms, Humidifier disinfectants, Cox proportional hazards model, Polyhexamethylene guanidine phosphate

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INTRODUCTION

Humidifier disinfectants, added to water in home humidifiers to prevent microbial growth and scale formation, were first introduced in the Korea in 1994. These over-the-counter biocides, available in 41 products [1], were widely used until 2011 [2]. Notably, unexplained fatal lung injuries were reported in children in 2006 [3], with similar cases emerging in adults in 2011 [2]. An epidemiological investigation by the Korea Disease Control and Prevention Agency identified a link between humidifier disinfectant use and lung injuries, including interstitial pneumonitis and extensive pulmonary fibrosis [4]. Consequently, the Korean govern-

ment banned the sale of these disinfectants and mandated their recall in 2011 [5].

Humidifier disinfectants contain various agents, including polyhexamethylene guanidine (PHMG; CAS No. 31961-54-3), oligo-(2-(2-ethoxy)-ethoxyethyl) guanidine (CAS No. 374572-91-5), and a combination of chloromethylisothiazolinone (CAS No. 26172-55-5) and methylisothiazolinone (CAS No. 2682-20-4). Among them, PHMG—a major component of these disinfectants that is commonly found in household products such as shampoos and moist towelettes [6,7]—has been designated by the International Agency for Research on Cancer as a high-priority agent for carcinogenicity evaluation [8]. Although animal studies increasingly demonstrate that PHMG exposure promotes lung cancer development [9], epidemiological investigations into the link between humidifier disinfectant use and lung cancer remain limited.

Therefore, this study aimed to evaluate the association between the duration of humidifier disinfectant use and the development of lung cancer among individuals who participated in Korean government surveys on humidifier disinfectant-related harm. To our knowledge, this represents one of the first epidemiological studies to investigate the potential impact of humidifier disinfectants on lung cancer. We anticipate that our findings will provide critical evidence establishing the carcinogenic potential of biocides used in these products.

MATERIALS AND METHODS

Study population

This study utilized data from Korean government surveys of individuals with a history of humidifier disinfectant use who filed compensation claims for associated health damage. Initially, only a few pre-specified diseases were eligible for compensation, among which lung cancer was not included. However, following a legal amendment in 2020, this limitation on diseases designated as related to humidifier disinfectant exposure was lifted. In most lung cancer cases (115 of 121 applicants), exposure assessments—including the duration of disinfectant use—were conducted before diagnosis.

Data were collected from claimants by the Korea Environmental Industry & Technology Institute [10], with the first survey initiated in July 2013. For this analysis, we included data from all surveys conducted through December 2021, the most recent available. Applicants whose data collection was complete were reviewed and registered for compensation by the Committee for the Determination of Humidifier Disinfectant-related Health Effects [10] under the “Special Act on Remedy for Damage Caused by Humidifier Disinfectants.” Trained occupational and environmental health nurses or industrial hygienists conducted standardized interviews to document humidifier disinfectant exposure, medical history, socio-demographic characteristics, lifestyle factors, household environment, and occupational exposures [11]. This study did not incorporate data from external sources such as the National Health Insurance Service, National Cancer Registry,

or Death Registry.

Among 7,032 applicants, 6,834 had not developed lung cancer by December 31, 2021, while 198 had developed lung cancer by that date. Of the 6,834 applicants without lung cancer, we excluded 409 individuals who lacked information on the date of initial humidifier disinfectant use, 289 who were missing information on duration of use, 25 who reported use before 1994, 4 whose recorded date of death preceded their initial use, 553 who died within 4 years of initial use, and 2,070 whose first exposure occurred at age 19 or younger. From the 198 applicants who developed lung cancer by December 31, 2021, we excluded 12 who lacked information on duration of use, 63 who were diagnosed with lung cancer or died within 4 years of initial use, and 2 who were first exposed at age 19 or younger. The final sample comprised 3,605 individuals, of whom 121 were diagnosed with lung cancer and 3,484 were not diagnosed (Figure 1).

Exposure to humidifier disinfectants

Humidifier disinfectant exposure was assessed using a standardized interview containing a series of exposure-related questionnaires. Among the investigated exposure variables—including duration of use, exposure history, product name, usage behavior, and distance from the humidifier—we selected duration of

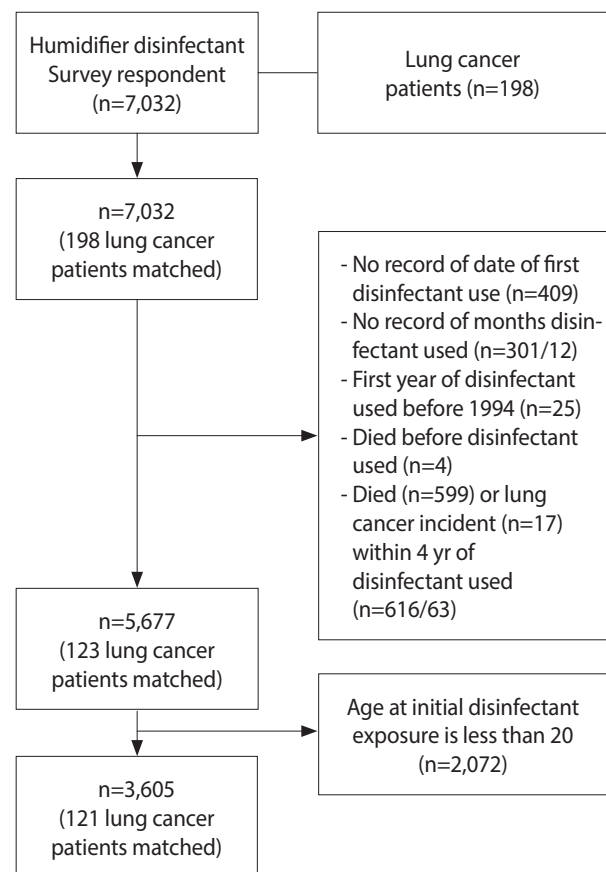


Figure 1. Flowchart of the study population.

use (in months) as the main exposure variable because it had the fewest missing values and outliers. Consistent with a previous study [12], we then categorized duration into 4 groups: <5 months, 5-14 months, 15-29 months, and ≥ 30 months.

Reported health conditions

After obtaining consent for the use of personal information, occupational and environmental medicine specialists commissioned by the Committee for the Determination of Humidifier Disinfectant-related Health Effects reviewed the applicants' medical records to confirm lung cancer diagnoses and to collect detailed information on the date of diagnosis, cancer stage, and prognosis/outcomes, including death.

We defined lung cancer cases as those first diagnosed at least 4 years after initial exposure to humidifier disinfectants [13,14]. We also repeated the analyses using extended latency periods of 6 years and 8 years.

Statistical analysis

Hazard ratios (HRs) and 95% confidence intervals (CIs) for lung cancer occurrence by duration of humidifier disinfectant use were estimated using Cox proportional hazards models. The baseline for the analyses was defined as the date of first humidifier disinfectant use, and follow-up continued until the earliest of: December 31, 2021; the date of lung cancer diagnosis (most recent case: April 8, 2020); or death. Individuals were censored at death if it occurred before December 31, 2021. We evaluated the proportional hazards assumption and confirmed that it was not violated ($p = 0.37$; Figure 2).

The Cox regression models were adjusted for sex, age at initial exposure (20-39, 40-49, or ≥ 50 years), education level (middle

school or lower, high school, or college or higher), tobacco smoking status (never smoked, current, or former smoker), and distance from the humidifier (<0.5, 0.5-0.9, 1.0-1.9 or ≥ 2.0 m).

Because humidifier disinfectant exposure and tobacco smoking are both major risk factors for lung cancer and may act synergistically [15], we constructed a joint exposure variable combining disinfectant use duration (<15 vs. ≥ 15 months) and smoking status (never, current, or former smoker). We then applied similar Cox regression models, adjusted for the covariates detailed above, to assess this joint association with lung cancer, using never smokers with <15 months of disinfectant use as the reference group. The relative excess risk due to interaction (RERI) was estimated using the delta method [16].

Stratified analyses were conducted by sex, age at initial exposure (20-49 vs. ≥ 50 years), and education level (high school or lower vs. college or higher) to assess potential heterogeneity in the association between disinfectant use duration and lung cancer development. Stratification by disinfectant ingredient and by smoking status was not performed because limited sample sizes precluded stable estimates.

To assess the sensitivity and robustness of our findings, we repeated the analyses using latency periods of 6 years and 8 years instead of 4 years.

All statistical analyses were performed using Stata version 18.0 MP (StataCorp., College Station, TX, USA), with a 2-sided p -value of less than 0.05 considered to indicate statistical significance.

Ethics statement

The study protocol was reviewed and approved by the Institutional Review Board of Severance Hospital (IRB No. 4-2024-

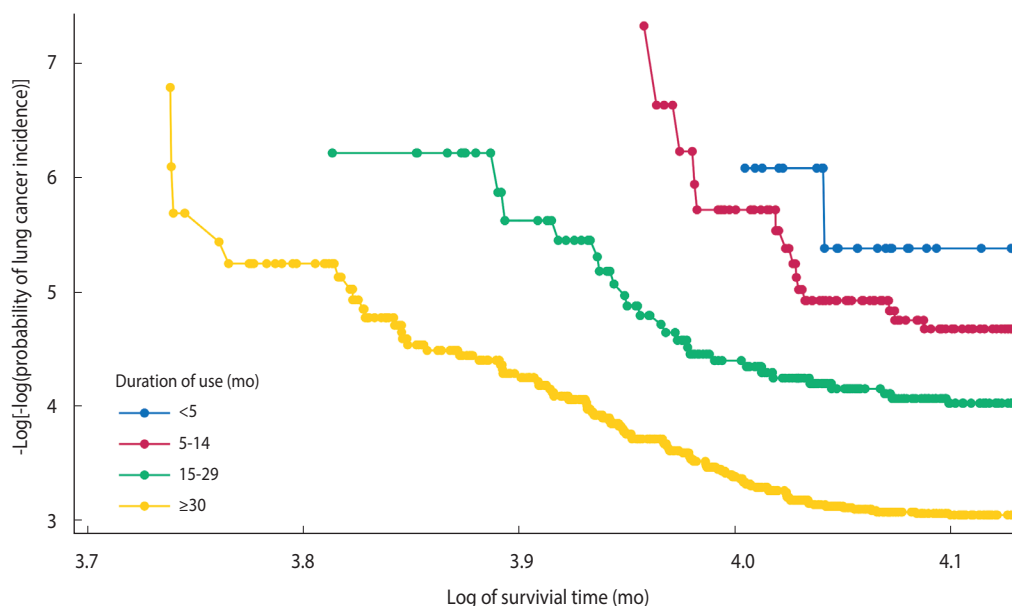


Figure 2. Log-log survival plot depicting the association between the duration of humidifier disinfectant use and lung cancer risk.

11194). Written informed consent was obtained from all compensation applicants or, for those under 19 years of age, from their parents.

RESULTS

Study population

Table 1 presents the general characteristics of the study population ($n = 3,605$), stratified by lung cancer status. Overall, 47.4% ($n = 1,707$) were male, 52.5% ($n = 1,892$) were first exposed to humidifier disinfectants between the ages of 20 years and 39 years, 52.2% ($n = 1,882$) had an education level of college or higher, and 66.2% ($n = 2,386$) had never smoked. The proportion of individuals who developed lung cancer was greater among those with a

middle school education or lower and among current or former smokers, relative to their counterparts with higher education or who never smoked.

Distribution of lung cancer development by exposure characteristics

The proportion of humidifier disinfectant use for at least 30 months was substantially higher among individuals diagnosed with lung cancer compared to those without this diagnosis (67.9 vs. 41.3%). In addition, those with lung cancer diagnoses tended to report shorter distances from the humidifier, although this difference was modest (Table 2).

The average duration of humidifier disinfectant use was longer among applicants diagnosed with lung cancer than among those

Table 1. Characteristics of the study population

Characteristics	Total	Lung cancer	No lung cancer	p-value ¹
Overall	3,605	121 (3.4)	3,484 (96.6)	
Sex				0.21
Male	1,707	64 (3.7)	1,643 (96.3)	
Female	1,898	57 (2.5)	1,841 (97.5)	
Age at initial exposure (yr)				0.14
20-39	1,892	37 (2.0)	1,855 (98.0)	
40-49	553	26 (4.7)	527 (95.3)	
≥50	1,160	58 (5.0)	1,102 (95.0)	
Education level				<0.01
Middle school or lower	689	35 (5.1)	654 (94.9)	
High school	1,034	39 (3.8)	995 (96.2)	
College or higher	1,882	47 (2.5)	1,835 (97.5)	
Tobacco smoking status				<0.01
Never smoker	2,386	66 (2.8)	2,320 (97.2)	
Current or former smoker	1,219	55 (4.5)	1,164 (95.5)	
Survival status (as of 2021)				<0.01
Survived	2,858	51 (1.8)	2,807 (98.2)	
Deceased	747	70 (9.4)	677 (90.6)	

Values are presented as number or number (%).

¹Using chi-square tests for sex and survival status and Cochran–Armitage trend tests for all other variables.

Table 2. Distribution of lung cancer development by exposure characteristics

Variables	Total ($n=3,605$)	Lung cancer ($n=121$)	No lung cancer ($n=3,484$)	p-value ¹
Duration of humidifier disinfectant use (mo)				<0.01
<5	240	2 (0.8)	238 (99.2)	
5-14	909	14 (1.5)	895 (98.5)	
15-29	934	23 (2.5)	911 (97.5)	
≥30	1,522	82 (5.4)	1,440 (94.6)	
Distance from humidifier (m)				0.02
<0.5	1,173	45 (3.8)	1,128 (96.2)	
0.5-0.9	1,304	54 (4.1)	1,250 (95.9)	
1.0-1.9	839	16 (1.9)	823 (98.1)	
≥2.0	276	6 (2.2)	270 (97.8)	

Values are presented as number or number (%).

¹Using Cochran–Armitage trend tests.

without such a diagnosis. The mean $\pm$ standard deviation duration of use was 53.4 ± 37.9 months in the lung cancer group versus 33.5 ± 31.9 months in the non-lung cancer group. The median durations were 45 months and 24 months for the lung cancer and non-lung cancer groups, respectively (Table 3).

Association between the duration of humidifier disinfectant use and lung cancer risk

The analysis included 53,966.2 person-years of observation, during which 121 incident lung cancer cases were identified. Compared with < 5 months of humidifier disinfectant use, the HRs for lung cancer incidence were 1.81 (95% CI, 0.41 to 7.97) for 5-14 months, 2.45 (95% CI, 0.58 to 10.41) for 15-29 months, and 4.61 (95% CI, 1.12 to 18.91) for ≥ 30 months. When duration of use was modeled as a continuous variable in the same analytical model, each additional month of use was associated with an HR of 1.01 (95% CI, 1.00 to 1.01) for lung cancer incidence (Table 4).

In the joint exposure analyses combining humidifier disinfectant use duration (< 15 vs. ≥ 15 months) and smoking status (never vs. current/former smoker), and using never smokers with < 15 months of use as the reference, the HRs of lung cancer incidence were 2.97 (95% CI, 1.34 to 6.56) for never smokers with ≥ 15 months of use, 2.73 (95% CI, 0.94 to 7.95) for current or former smokers with < 15 months of use, and 4.74 (95% CI, 1.94 to 11.61) for current or former smokers with ≥ 15 months of use. We found no evidence of interaction between the duration of humidifier disinfectant use and smoking status (RERI, 0.04; 95% CI, -2.57 to 2.65).

Table 3. Distribution of humidifier disinfectant use duration among the study population

Humidifier disinfectant usage period (mo)	Mean $\pm$ SD	Min	Median	Max
Total	34.2 $\pm$ 32.3	0.1	24	221
Lung cancer	53.4 $\pm$ 37.9	1.0	45	180
No lung cancer	33.5 $\pm$ 31.9	0.1	24	221

SD, standard deviation; Min, minimum; Max, maximum.

In the analyses stratified by sex, age at initial exposure (20-49 vs. ≥ 50 years), and education level (high school or lower vs. college or higher), we observed consistent, monotonic dose-response relationships between disinfectant use duration and lung cancer risk across all strata. However, no statistically significant associations were detected within a stratum, likely due to the small sample sizes. Furthermore, the CIs overlapped across groups, indicating no appreciable heterogeneity across these stratifying variables. Nevertheless, point estimates were relatively high among males, individuals first exposed to humidifier disinfectant at 20-49 years of age, and those with a college education or higher (Figure 3, Supplementary Material 1).

In the sensitivity analyses using extended latency periods of 6 years and 8 years, we observed similar monotonic associations between disinfectant use duration and lung cancer risk, although the strength of these associations attenuated with longer latency (Supplementary Material 2).

DISCUSSION

In this study, prolonged use of humidifier disinfectants was associated with a dose-response increase in lung cancer risk, even after adjusting for key covariates such as tobacco smoking. Specifically, compared with < 5 months of use, the HR for lung cancer was significantly greater for ≥ 30 months, with the point estimate exceeding 4. These results provide robust epidemiological evidence for the role of humidifier disinfectants in lung cancer development, consistent with findings from prior animal studies.

Although lung cancer incidence was higher in our study population compared to the general population, previously established risk factors for lung cancer (e.g., lower educational attainment and tobacco smoking) were similarly associated with increased lung cancer risk in this study (Table 1). Moreover, we observed a dose-response relationship between humidifier disinfectant exposure and lung cancer (Tables 2 and 3, Figures 2 and 3). Collectively, these findings can be interpreted as supporting the association between humidifier disinfectant use and lung cancer risk, an association unlikely to be explained solely by selection bias within

Table 4. HRs and 95% CIs for lung cancer occurrence by duration of humidifier disinfectant use¹

Duration (mo)	n	Person-years	Lung cancer	Mean $\pm$ SD (yr) ²	HR (95% CI)
Categorical variable					
<5	240	3,042.5	2	52.4 $\pm$ 13.4	1.00 (reference)
5-14	909	12,215.4	14	53.1 $\pm$ 12.8	1.81 (0.41, 7.97)
15-29	934	13,518.7	23	55.3 $\pm$ 13.2	2.45 (0.58, 10.41)
≥ 30	1,522	25,189.4	82	59.4 $\pm$ 13.2	4.61 (1.12, 18.91)
Continuous variable					
Per-1	3,605	53,966.2	121	56.3 $\pm$ 13.4	1.01 (1.00, 1.01)

HR, hazard ratio; CI, confidence interval; SD, standard deviation.

¹The results were analyzed using Cox proportional hazards models adjusted for sex, age at initial exposure, education level, tobacco smoking status, and distance from the humidifier.

²Mean age at the end of follow-up.

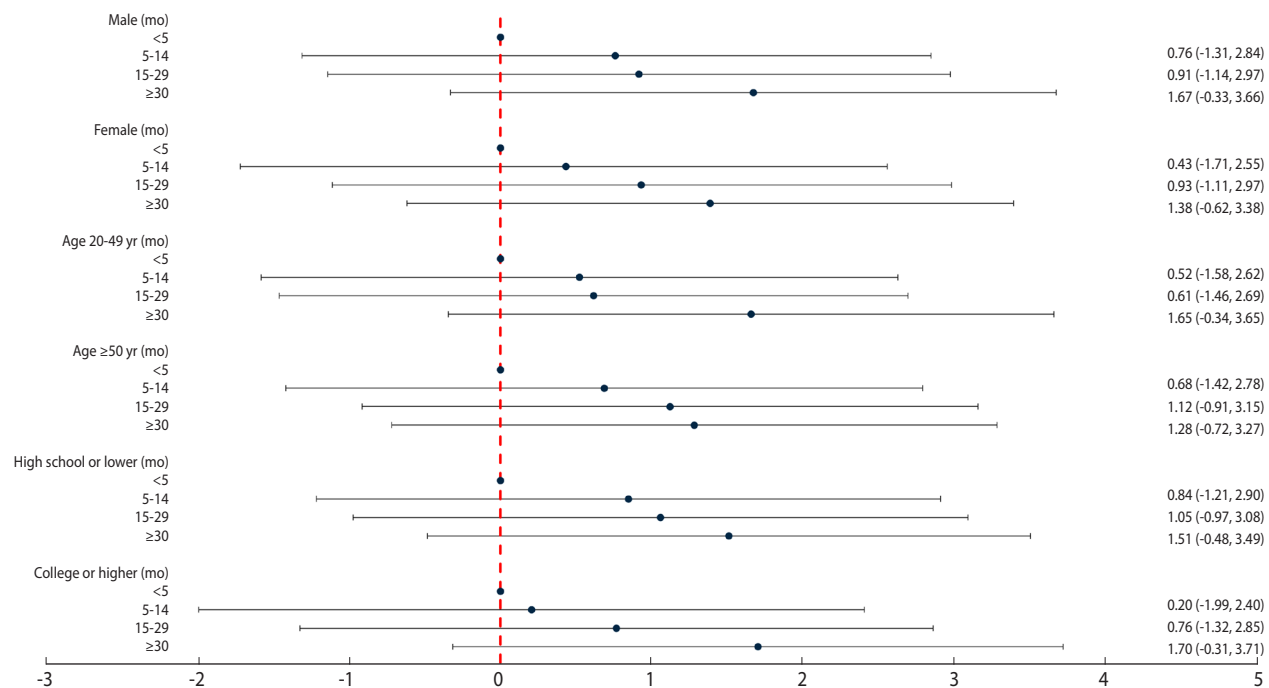


Figure 3. Associations between the duration of humidifier disinfectant use and lung cancer risk, stratified by sex, age at initial exposure (20-49 yr. vs. ≥50 years), and education level (high school or lower vs. college or higher). The results are presented as natural log-transformed hazard ratios with corresponding log-transformed 95% confidence intervals.

this study population.

Several animal studies have demonstrated that PHMG—a major ingredient in humidifier disinfectants—promotes lung carcinogenesis. For example, exposure to PHMG phosphate (PHMG-p), a common form of PHMG, increased the risk of lung cancer even after the cessation of respiratory exposure, yielding a 73.7% incidence rate in rats at high doses. That study also reported that PHMG-p exposure induced lung inflammation, fibrosis, precancerous lesions, and somatic mutations in lung cancer-related genes such as *TP53* [17]. In mice, intratracheal administration of a PHMG solution resulted in bronchoalveolar adenomas in 50% of animals within 6-8 weeks, along with genetic alterations associated with lung cancer [9]. Similarly, a single intratracheal instillation of PHMG induced lung carcinoma and progressive fibrosis in rats [18,19].

The observed association between humidifier disinfectant use duration and lung cancer development may in part reflect the reported link between humidifier disinfectant exposure and interstitial lung disease (ILD). ILD is strongly associated with lung cancer [20] due to overlapping biological processes, such as fibrogenesis and carcinogenesis, as well as shared risk factors [21,22]. Epidemiological studies have revealed a significant relationship between humidifier disinfectant exposure and the risk of ILD, along with ILD-related features like ground-glass opacities, centrilobular fibrosis, and air leakage [23]. Similarly, an animal study in rats demonstrated that humidifier disinfectant exposure induces lung fibrosis and inflammatory responses resembling ILD-like

pathology [24]. Together, these findings further support the link between disinfectant use duration and lung cancer development observed in this study.

Within the aggregate exposure pathway-adverse outcome pathway (AEP-AOP) framework, humidifier disinfectant chemicals such as PHMG have been shown to induce a cascade of events, including oxidative stress, inflammation, epithelial damage, and necrosis, that culminate in severe clinical outcomes like ILD and lung cancer [25]. PHMG-p drives lung carcinogenesis primarily through non-genotoxic mechanisms, including chronic inflammation, apoptosis, and secondary DNA damage [26]. Furthermore, prolonged PHMG-p exposure alters the expression of lung cancer-associated genes in human pulmonary alveolar epithelial cells, underscoring its carcinogenic potential [27].

We observed no evidence of interaction between the duration of humidifier disinfectant use and tobacco smoking for lung cancer risk. To our knowledge, this is the first study to examine this potential interaction, and our finding thus warrants validation in future research. However, the independent associations of disinfectant exposure and smoking with lung cancer suggest distinct biological pathways for these risk factors. Given the substantial overlap between the previously described AEP-AOP and the carcinogenic pathways of tobacco smoke, further mechanistic studies are needed to delineate the pathways associated with humidifier disinfectant exposure.

This study had several limitations. First, the study population consisted of individuals exposed to humidifier disinfectants who

reported at least 1 health condition when registering for government compensation, raising concerns about selection bias and limiting generalizability. However, lung cancer was only recently recognized as a compensable disease for claims related to humidifier disinfectant exposure. Thus, participants were not enrolled specifically because of a lung cancer diagnosis. Furthermore, animal studies demonstrating a causal relationship between humidifier disinfectant exposure and lung cancer suggest that our findings cannot be entirely explained by selection or collider stratification bias. Future epidemiological investigations using diverse populations, study designs, and analytic methods robust to selection bias—such as propensity score techniques and instrumental variable approaches—are warranted to confirm our results. Second, exposure assessment relied on self-reported data, introducing the possibility of recall bias. Although well-structured interviews with logical and repetitive questioning were conducted to mitigate this concern, differential misclassification based on health status (e.g., symptom severity) may still have inflated associations. Third, because of the long latency between exposure and lung cancer onset, cancer may have manifested only in a subset of at-risk individuals, despite a follow-up period of over 10 years. Consequently, the incidence may continue to rise, particularly among those exposed to humidifier disinfectants at younger ages.

Nonetheless, the present study has several strengths. First, it is among the first epidemiological investigations to offer robust evidence linking prolonged humidifier disinfectant use to an elevated risk of lung cancer. Although animal studies had previously supported this association, epidemiological research remains limited. Second, lung cancer diagnoses were confirmed by physicians through medical record review, minimizing the risk of outcome misclassification and ensuring that the results reflect verified diagnoses. Third, this study was adjusted for key lung cancer risk factors, including smoking status, and also evaluated the potential synergistic interaction between disinfectant use duration and smoking in lung cancer development.

In conclusion, prolonged use of humidifier disinfectants was associated with a dose-dependent increase in lung cancer risk. Compared with < 5 months of use, individuals with ≥ 30 months of exposure had a HR exceeding 4 for lung cancer. These findings provide compelling epidemiological evidence supporting the role of prolonged humidifier disinfectant use in the development of lung cancer. However, further research—including studies involving unexposed populations—is needed to validate these results.

NOTES

Supplementary materials

Supplementary materials are available at <https://doi.org/10.4178/epih.e2025023>.

Conflict of interest

The authors have no conflicts of interest to declare for this study.

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Author contributions

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REFERENCES

1. Korea Centers for Disease Control and Prevention. Interim report of epidemiological investigation on lung injury with unknown cause in Korea. Public Health Wkly Rep 2011;4:817-818 (Korean).
2. Hong SB, Kim HJ, Huh JW, Do KH, Jang SJ, Song JS, et al. A cluster of lung injury associated with home humidifier use: clinical, radiological and pathological description of a new syndrome. Thorax 2014;69:694-702. <https://doi.org/10.1136/thoraxjnl-2013-204135>
3. Park DU, Ryu SH, Roh HS, Lee E, Cho HJ, Yoon J, et al. Association of high-level humidifier disinfectant exposure with lung injury in preschool children. Sci Total Environ 2018;616-617:855-862. <https://doi.org/10.1016/j.scitotenv.2017.10.237>
4. Lung Injury Investigation Committee. White paper on the health damage disaster from humidifier disinfectants. Sejong: Ministry of Health and Welfare; 2014. p. 12-99 (Korean).
5. Byeon J, Kim HS, Park MY, Lee KM, Hong MG, Choi YY. An estimation of population at risk of exposure to humidifier disinfectant and associated health effects. J Environ Health Sci 2020;46:

- 457-469 (Korean). <https://doi.org/10.5668/JEHS.2020.46.4.457>
6. Vitt A, Sofrata A, Slizen V, Sugars RV, Gustafsson A, Gudkova EI, et al. Antimicrobial activity of polyhexamethylene guanidine phosphate in comparison to chlorhexidine using the quantitative suspension method. *Ann Clin Microbiol Antimicrob* 2015;14:36. <https://doi.org/10.1186/s12941-015-0097-x>
7. Ohta S, Misawa Y, Miyamoto H, Makino M, Nagai K, Shiraishi T, et al. A comparative study of characteristics of current-type and conventional-type cationic bactericides. *Biol Pharm Bull* 2001;24:1093-1096. <https://doi.org/10.1248/bpb.24.1093>
8. Berrington de González A, Masten SA, Bhatti P, Fortner RT, Peters S, Santonen T, et al. Advisory Group recommendations on priorities for the IARC Monographs. *Lancet Oncol* 2024;25:546-548. [https://doi.org/10.1016/S1470-2045\(24\)00208-0](https://doi.org/10.1016/S1470-2045(24)00208-0)
9. Kim C, Jeong SH, Kim J, Lee KY, Cha J, Lee CH, et al. Evaluation of polyhexamethylene guanidine-induced lung injuries by chest CT, pathologic examination, and RNA sequencing in a rat model. *Sci Rep* 2021;11:6318. <https://doi.org/10.1038/s41598-021-85662-z>
10. Korea Environmental Industry and Technology Institute (KEITI). Comprehensive portal for humidifier disinfectant damage support: statistics [cited 2023 May 3]. Available from: <https://www.healthrelief.or.kr/home/content/stats01/view.do> (Korean).
11. Choi YH, Ryu H, Yoon J, Lee S, Kwak JH, Han BY, et al. Demographic characteristics and exposure assessment for applicants who have been injured by humidifier disinfectant-focusing on 4-1 and 4-2 applicants. *J Environ Health Sci* 2018;44:301-314 (Korean). <https://doi.org/10.5668/JEHS.2018.44.4.301>
12. Hong M, Ju MJ, Yoon J, Lee W, Lee S, Jo EK, et al. Exposures to humidifier disinfectant and various health conditions in Korean based on personal exposure assessment data of claimants for compensation. *BMC Public Health* 2023;23:1800. <https://doi.org/10.1186/s12889-023-16389-x>
13. Marinaccio A, Binazzi A, Cauzillo G, Cavone D, Zotti RD, Ferrante P, et al. Analysis of latency time and its determinants in asbestos related malignant mesothelioma cases of the Italian register. *Eur J Cancer* 2007;43:2722-2728. <https://doi.org/10.1016/j.ejca.2007.09.018>
14. Frost G. The latency period of mesothelioma among a cohort of British asbestos workers (1978-2005). *Br J Cancer* 2013;109:1965-1973. <https://doi.org/10.1038/bjc.2013.514>
15. Jee SH, Samet JM, Ohrr H, Kim JH, Kim IS. Smoking and cancer risk in Korean men and women. *Cancer Causes Control* 2004;15:341-348. <https://doi.org/10.1023/B:CACO.0000027481.48153.97>
16. Andersson T, Alfredsson L, Källberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. *Eur J Epidemiol* 2005;20:575-579. <https://doi.org/10.1007/s10654-005-7835-x>
17. Lee H, Jeong SH, Baek YW, Lee H, Sa JK, Lee JY, et al. Deciphering the toxicity of polyhexamethylene guanidine phosphate in lung carcinogenesis: mutational profiles and molecular mechanisms. *Chemosphere* 2024;368:143785. <https://doi.org/10.1016/j.chemosphere.2024.143785>
18. Kim C, Jeong SH, Kim J, Kang JY, Nam YJ, Togloom A, et al. Evaluation of the long-term effect of polyhexamethylene guanidine phosphate in a rat lung model using conventional chest computed tomography with histopathologic analysis. *PLoS One* 2021;16:e0256756. <https://doi.org/10.1371/journal.pone.0256756>
19. Park DU, Ryu SH, Lim HK, Kim SK, Choi YY, Ahn JJ, et al. Types of household humidifier disinfectant and associated risk of lung injury (HDLI) in South Korea. *Sci Total Environ* 2017;596-597:53-60. <https://doi.org/10.1016/j.scitotenv.2017.04.040>
20. Gibiot Q, Monnet I, Levy P, Brun AL, Antoine M, Chouaïd C, et al. Interstitial lung disease associated with lung cancer: a case-control study. *J Clin Med* 2020;9:700. <https://doi.org/10.3390/jcm9030700>
21. Dasgupta S. Identification of hub genes in interstitial lung disease and their association with lung cancer: an in-silico analysis. In: 2024 International Conference on Computer, Electrical & Communication Engineering (ICCECE). Kolkata: IEEE; 2024, p. 1-8. <https://doi.org/10.1109/ICCECE58645.2024.10497218>
22. Naccache JM, Gibiot Q, Monnet I, Antoine M, Wislez M, Chouaïd C, et al. Lung cancer and interstitial lung disease: a literature review. *J Thorac Dis* 2018;10:3829-3844. <https://doi.org/10.21037/jtd.2018.05.75>
23. Yang HJ, Kim HJ, Yu J, Lee E, Jung YH, Kim HY, et al. Inhalation toxicity of humidifier disinfectants as a risk factor of children's interstitial lung disease in Korea: a case-control study. *PLoS One* 2013;8:e64430. <https://doi.org/10.1371/journal.pone.0064430>
24. Park S, Lee K, Lee EJ, Lee SY, In KH, Kim HK, et al. Humidifier disinfectant-associated interstitial lung disease in an animal model induced by polyhexamethylene guanidine aerosol. *Am J Respir Crit Care Med* 2014;190:706-708. <https://doi.org/10.1164/rccm.201404-0710LE>
25. Kim HR, Kim JW, Lee JH, Kim Y, Lim J, Baek YW, et al. Toxicological evidence integration to confirm the biological plausibility of the association between humidifier disinfectant exposure and respiratory diseases using the AEP-AOP framework. *Epidemiol Health* 2024;46:e2024060. <https://doi.org/10.4178/epih.e2024060>
26. Park YJ, Kim HR, Kim JW, Lee JH, Kim Y, Lim J, et al. Comprehensive analysis of adverse outcome pathway, potency, human exposure supports carcinogenicity of polyhexamethylene guanidine phosphate in lung cancer. *Ecotoxicol Environ Saf* 2024;287:117222. <https://doi.org/10.1016/j.ecoenv.2024.117222>
27. Lee H, Jeong SH, Lee H, Kim C, Nam YJ, Kang JY, et al. Analysis of lung cancer-related genetic changes in long-term and low-dose polyhexamethylene guanidine phosphate (PHMG-p) treated human pulmonary alveolar epithelial cells. *BMC Pharmacol Toxicol* 2022;23:19. <https://doi.org/10.1186/s40360-022-00559-5>