

BRIEF REPORT

Possibility of lung cancer risk in indium-exposed workers: An 11-year multicenter cohort study

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Abstract

Background: We established a causal relationship between indium exposure and lung interstitial and emphysematous effects. Lung cancer has been clearly demonstrated in rats and mice exposed to indium phosphide and in rats exposed to indium tin oxide. However, no information is available on human indium-related lung cancer.

Methods: The baseline studies were conducted on 381 indium-exposed and 150 referent workers in 11 factories from 2003 to 2006. Items examined included indium concentration in serum (In-S), occupational history, Krebs von den Lungen-6 (KL-6), chest high-resolution computed tomography (HRCT), medical history, smoking habits, and subjective symptoms. Subjects received follow-up health checkups, and a total of 220 indium-exposed and 26 nonexposed workers were examined at least once with chest HRCT from 2013 to 2018.

Results: Four lung cancer cases were identified only in indium-exposed workers. Two were prevalent cases and two were incident cases. The averages (range) of age (years), exposure duration (years), In-S ($\mu\text{g/L}$), and KL-6 (U/mL) at the baseline survey were 58 (50-74), 1.7 (0.3-4.8), 3.1 (0.3-9.7), and 663 (414-942). The mean (range) latency from initial indium exposure was 5.3 (0.4-11) years. The HRCT findings in two incident cases were mild interstitial/emphysematous change and mild interstitial change. The standardized incidence ratio (SIR) of the incident cases was 1.89 (95%CI 0.52-6.88).

Conclusions: Although the SIR was not statistically significant, there was an undeniable possibility of indium-related lung cancer due to the short follow-up duration being insufficient to disclose lung cancer and the small number of lung cancer cases. Further follow-up is necessary.

KEYWORDS

cohort study, human, indium, ITO, lung cancer

Abbreviations: BEL, Biological Exposure Limit; HRCT, high-resolution computed tomography; InP, indium phosphide; In-S, indium concentration in serum; ITO, indium-tin oxide; JMHLW, Japanese Ministry of Health Labour and Welfare; KL-6, Krebs von den Lungen-6; SIR, standardized incidence ratio; SP-D, surfactant protein D.

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1 | INTRODUCTION

After the first fatal case of interstitial pneumonia due to indium exposure in 2001,¹ a causal relationship was established between indium exposure and lung interstitial² and emphysematous^{3,4} effects by epidemiological studies. Hardly soluble indium phosphide (InP)⁵ and indium tin oxide (ITO)⁶ showed lung carcinogenicity in a significantly dose-dependent manner by 2-year inhalation studies in rats and/or mice. In 2010, the Japanese Ministry of Health, Labour and Welfare (JMHLW) issued technical guideline for preventing health impairment of workers engaged in the ITO handling processes based on these reports.⁷ The Japan Society for Occupational Health proposed a Biological Exposure Limit (BEL) of 3 µg/L serum indium in 2007 and classified indium compounds (inorganic, hardly soluble) as Group 2A carcinogens (probably carcinogenic to humans) in 2014.⁸ The International Agency for Research on Cancer proposed InP as 2A⁹ and ITO as 2B¹⁰ in 2006 and 2017, respectively. In 2018, the American Conference of Governmental Industrial Hygienists proposed new threshold limit values of 0.1 µg/m³ for ITO respirable dust and placed it on the “notice of intended changes” list.¹¹ It is likely that the human carcinogenicity of indium compounds will soon be a novel topic of research interest. However, to the best of our knowledge, lung carcinogenicity in humans has not yet been reported. In this article, we discuss lung cancer cases observed in an 11-year multicenter cohort study.

2 | METHODS

We conducted a baseline survey of 383 exposed workers and 159 nonexposed workers in 11 indium-handling factories from 2003 and 2006.³ Items examined included indium concentration in serum (In-S), occupational history, Krebs von den Lungen-6 (KL-6), and surfactant protein D (SP-D) as interstitial pneumonia markers, pulmonary function tests, chest high-resolution computed tomography (HRCT), medical history, smoking habits, and subjective symptoms using the Japanese version of the American Thoracic Society Division of Lung Disease questionnaire and supplementary questions. The In-S levels of two exposed and seven nonexposed workers were missing, and the In-S levels of two nonexposed workers were suspected to be contaminated. The final numbers of workers who underwent the baseline survey included 381 exposed and 150 nonexposed workers, and they were followed up between 2013 and 2018. During the follow-up period, 23 nonexposed workers transferred to indium-exposed job sites. Figure S1 shows the follow-up flow of the study subjects.

Two hundred and twenty indium-exposed workers (male, 204) and 26 referent workers (male, 25) were traced from the baseline survey to the last survey. The mean follow-up duration was 11.1 years. All followed up subjects were examined at least one with chest HRCT during the follow-up period. The diagnosis of lung cancer was confirmed by medical certificate to the extent possible.

The follow-up duration of each exposed worker was defined to be from the baseline survey to the year of diagnosis of lung cancer or the last survey, whichever came first. An expected number of lung cancer cases in the exposed worker cohort was calculated using the male, calendar year, and 5-year age-specific incidence rates of lung cancer in the general male population in Japan.¹² The observed number was the incident lung cancer cases that occurred during the follow-up period.

This study was approved by the Ethics Committee of Keio University School of Medicine, and all individuals gave informed consent. In a fatal case, we obtained informed consent from family members.

3 | RESULTS

At the baseline survey, two prevalent lung cancer cases (Case 1 and Case 2) were disclosed only in the exposed workers. In 2009, we requested current medical histories of the study subjects to the factory staffs and knew that one exposed worker died by lung cancer (Case 3) in 2006. At a follow-up health checkup in 2015, one exposed worker informed us that he had been diagnosed with lung cancer in 2014 (Case 4) and his chest HRCT showed a finding after lobectomy for lung cancer. Another exposed worker (Case 5) was not a cohort member in this study, but he had undergone measurements of In-S, KL-6, and SP-D in 2007. At the time of the follow-up survey, his family informed us that he had died due to lung cancer in 2015. With consent from his family, we obtained a medical certificate from his doctor and confirmed that he had lung cancer. As Case 5 was not a cohort member, we excluded him from the statistical analysis but included him in the case presentation.

Table 1 shows the characteristics, exposure levels, biomarkers for interstitial change, and chest HRCT findings of nonexposed subjects, indium-exposed subjects, and four lung cancer cases at the baseline survey. The four cases were older than other exposed workers and their exposure duration was shorter than that of other exposed workers. KL-6 in all cases fell into the fourth quartile (KL-6 ≥ 414 U/mL) of the entire study population.

Table 2 lists the characteristics, indium exposure levels, biomarkers for interstitial change, and pathological types and stages of the five lung cancer cases. The five cases occurred

TABLE 1 Characteristics, exposure levels, biomarkers, and chest high-resolution computed tomography (HRCT) of nonexposed, indium-exposed, and diseased subjects at the baseline survey

	Nonexposed (n = 150)	Exposed (n = 377)	Incident Cases ^a (n = 2)	All Cases ^b (n = 4)
Age, y (SD)	40.9 (11.8)	38.0 (12.0)	55.0 (11.3)	58.0 (7.4)
Category, n (%)				
19-29	34 (22.7)	102 (27.1)	0 (0.0)	0 (0.0)
30-39	35 (23.3)	132 (35.0)	0 (0.0)	0 (0.0)
40-49	34 (22.7)	70 (18.6)	1 (50.0)	1 (25.0)
50-59	40 (26.7)	49 (13.0)	0 (0.0)	0 (0.0)
60-70	6 (4.0)	23 (6.1)	1 (50.0)	3 (75.0)
Missing	1 (0.7)	1 (0.3)	0 (0.0)	0 (0.0)
Male, n (%)	120 (80.0)	346 (91.8)	2 (100)	4 (100)
Duration, year (SD) from initial exposure	—	4.9 (5.3)	1.0 (0.1)	1.7 (2.0)
Serum indium, In-S, µg/L (range)	0.6 (<0.1-3.0)	8.6 (<0.1-117)	1.0 (0.3-1.7)	3.1 (0.3-9.7)
Smoking, n (%)				
Never smokers	50 (33.3)	112 (29.7)	1 (50.0)	3 (75.0)
Ex-smokers	33 (22.0)	51 (13.5)	0 (0.0)	0 (0.0)
Current smokers	67 (44.7)	214 (56.8)	1 (50.0)	1 (25.0)
Biomarkers of effect, n (%)				
KL-6, U/ml				
Quartile 1 (92-193)	49 (32.7)	83 (22.0)	0 (0.0)	0 (0.0)
Quartile 2 (194-258)	48 (32.0)	85 (22.5)	0 (0.0)	0 (0.0)
Quartile 3 (259-413)	44 (29.3)	88 (23.3)	0 (0.0)	0 (0.0)
Quartile 4 (414-8140)	9 (6.0)	121 (32.1)	2 (100)	4 (100)
SP-D, ng/mL				
Quartile 1 (<17.2-35.3)	43 (28.7)	89 (23.6)	0 (0.0)	0 (0.0)
Quartile 2 (35.4-53.8)	44 (29.3)	88 (23.3)	1 (50.0)	1 (25.0)
Quartile 3 (54.0-83.6)	38 (25.3)	94 (24.9)	0 (0.0)	1 (25.0)
Quartile 4 (84.3-520)	25 (16.7)	106 (28.1)	1 (50.0)	2 (50.0)
HRCT findings, n ^c (%)				
Interstitial change	13 (11.1)	43 (23.1)	2 (100)	2 (50.0)
Emphysematous change	5 (4.3)	19 (10.2)	1 (50.0)	1 (25.0)

^aCases 3 and 4.^bCases 1-4.^cNumber of nonexposed, exposed, and diseased workers are 117, 186, and 4 (total 307), respectively.

at five different factories. All were males, with an average age of 64 years (range 50-75) and had no other history of dust exposure possibly affected their lungs. Two were smokers and Case 5 was an extremely heavy smoker (171 pack-years). Their jobs were as follows: two worked with a molding process of indium oxide and tin oxide mixed powder; one performed an ITO grinding process; and two worked an ITO waste plate recycling process. The mean duration of indium exposure was 2.1 years (range 0.3-4.8). Mean In-S in their baseline survey was 4.5 µg/L and In-S of three cases was less than 3 µg/L recommended the BEL by JSOH.⁸ Mean KL-6 level was 654 U/mL (range 414-942), and mean SP-D level

was 100 ng/mL (range 52-162). Mean latency from initial indium exposure was 9.1 years (range 0.4-24). When excluding one case of 0.4 years since an initial exposure, the mean latency was 11.2 years.

Pathological types (stages) of lung cancer were one bronchioloalveolar carcinoma¹³ (stage IA; T1aN0M0, Right S3), two adenocarcinoma, and two unknown due to the information being unavailable. The findings on chest HRCT at the baseline survey in Case 3 showed small centrilobular node, interlobular septal thickening throughout the lungs (<10%/Slice), ground glass opacity in the bilateral lower lung field (<50%/Slice), and paraseptal and centrilobular emphysematous

TABLE 2 The characteristics and occupational history of the worker in each lung cancer case

	Case 1	Case 2 ^d	Case 3	Case 4	Case 5 ^a
Information collection timing	First survey	First survey	Follow-up survey	Follow-up survey	
Age at diagnosis	60	62	50	74	75
Smoking history	Nonsmoker	Non-smoker	1 pack-25 y	Nonsmoker	3 pack-57 y
Job type	ITO waste plate recycling	ITO waste plate grinding/recycling	Molding ^b (dry)	Molding ^b (dry/wet)	ITO grinding
Indium exposure duration, y	0.3	4.8	1.0	3.2	1.0
In-S at baseline (µg/L)	0.7	9.7	0.3	1.7	10.1
KL-6 at baseline (U/mL)	414	942	447	847	620
SP-D at baseline (ng/mL)	56.8	141	52	162	88.3
Finding on chest high-resolution computed tomography (HRCT) at baseline					
Interstitial change	None ^c	None ^d	<10%/Slice	<5%/Slice	NA
Emphysematous change	None ^c	None ^d	<5%/Slice	None	NA
Latency from initial indium exposure, y	0.4	4.8	5	11	24
Pathological types and stages of lung cancer	Adenocarcinoma/1A	Bronchioloalveolar carcinoma/1A	NA	NA	Adenocarcinoma/4

NA: Not available.

^aCase 5 is non-cohort member.

^bIndium oxide and tin oxide molding.

^cThe findings of chest HRCT showed neither interstitial nor emphysematous changes at three lung levels (the upper, middle, and lower lung fields); however, lung cancer on other slices was pointed out.

^dReference 13. The findings showed neither interstitial nor emphysematous changes; however, a ground glass opacity (small nodular shadow) was shown in the right upper lobe.

change (<5%/Slice) in the same area as bullae (<5%/Slice) in the bilateral upper lung field and right middle lung field. The findings at the baseline survey in Case 4 showed small centrilobular node and interlobular septal thickening throughout the lungs (<5%/Slice), but no emphysematous changes. Case 5 has not undergone chest CT.

The expected number of lung cancer cases calculated for the Japanese general population was 1.06, and the SIR was 1.89 (2/1.06) (95% confidence interval 0.52-6.88).

4 | DISCUSSION

This is the first report of lung cancer in a multicenter cohort study. Lung cancer cases occurred only in indium-exposed workers. We confirmed five cases of lung cancer in the course of 11 years of observation.

Lung carcinogenicity in rats and/or mice exposed to hardly soluble InP and ITO has been clearly demonstrated, and showed a dose-dependent relationship between exposure concentration and incidence of lung carcinoma.^{5,6} However, no information is available on human indium-related lung cancer.

Latency is important for assessing any causal relationship between exposure and occupational cancer. Occupational lung cancer mostly occurs after a latent duration of at least

10 years. Based on this knowledge, Case 1 was not considered to be associated with indium exposure, since the latency as well as the duration of indium exposure was very short. The In-S levels for the two cases (Case 4 and Case 5) with the latency of more than 10 years were 1.7 and 10.1 µg/L, respectively. Although the In-S level (1.7 µg/L) in Case 4, who never smoked, was less than the BEL,⁸ the level of KL-6 was high (847 U/mL). As this indicates interstitial inflammation in the lungs, we were concerned that lung cancer might occur at an In-S of 1.0-2.9 µg/L. Case 5, a non-cohort member, was a 75-year-old extremely heavy smoker. While this case's duration of indium exposure was as short as 1 year, the In-S level measured 16 years after the cessation of indium exposure was as high as 10.1 µg/L. It is presumed that this patient was a short-term highly exposed case, so it is difficult to conclude that the causality of lung cancer in this case was smoking alone.

Although the SIR of lung cancer was 1.89 (95% CI 0.52-6.88) and was not statistically significant, it may be rash to conclude that this represents a negative result. Firstly, pulmonary inflammation and pulmonary diseases, including interstitial lung diseases, are known to be a risk for lung cancer,¹⁴ and indium-exposed workers showed interstitial changes on chest HRCT and elevation of KL-6 and SP-D² which are unique serum markers of interstitial pneumonia. In the five lung cancer cases, KL-6 and SP-D were high, and KL-6 in all cases

fell into the fourth quartile ($KL-6 \geq 414$ U/mL). Secondly, the estimated half-life of In-S was 8 years⁴ and indium compounds would have to remain in the lungs for a long time. Thirdly, the observation period of this cohort was not long enough to assess a causal relationship between indium exposure and lung cancer. Finally, a 2-year inhalation study of InP in rats and mice revealed the presence of lung cancer, and a carcinogenic mechanism was proposed. InP inhalation demonstrated the development of oxidative stress, identified by elevated levels of inducible nitric oxide synthase, cyclooxygenase-2, glutathione-S-transferase Pi, and 8-hydroxydeoxyguanosine, resulting in pulmonary inflammation in progression to atypical hyperplasia and lung cancer.⁵ Mouse macrophages with indium oxide in vitro suggested that endocytosis and NO generation participate in indium-induced 8-nitroguanine (a mutagenic DNA lesion formed during inflammation formation).¹⁵ These results suggest that inhalation of indium compounds, causing pulmonary inflammation associated with oxidative stress, endocytosis, and NO released from indium-exposed inflammatory cells, may induce DNA damage in adjacent lung epithelial cells and contribute to carcinogenesis. However, the development of interstitial fibrotic changes and its relationship with the carcinogenesis needs to be further explored.

This study had several limitations. First, the number of cases was small, and the duration of indium exposure was short in most cases. Next, we may not have been able to track the incidence of all lung cancer. Finally, the follow-up period was about 11 years, and further long-term observation will be very important.

5 | CONCLUSIONS

Although the SIR was not statistically significant, there was an undeniable possibility of indium-related lung cancer due to the short follow-up duration being insufficient to disclose lung cancer and the small number of lung cancer cases. Further follow-up is necessary.

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DISCLOSURE

Approval of the research protocol: This study was approved by the Ethics Committee of Keio University School of

Medicine (approval number 15-46 and 20110268). *Informed consent:* All individuals gave informed consent. In a fatal case, we obtained informed consent from family members. *Registry and the Registration no. of the study/Trial:* N/A. *Animal studies:* N/A. *Conflict of interest:* Authors declare no conflict of interests for this article.

AUTHOR CONTRIBUTIONS

M.N. takes responsibility for the integrity and accuracy of the data and manuscript. M.N. had primary responsibility for the design of the study and drafting of the article; contributed to fieldwork management; and contributed to acquisition, analysis, and interpretation of data and to critical revision of the manuscript. K.O had primary responsibility for the conception and design of the study and contributed to fieldwork management and interpretation of data and to critical revision of the manuscript. M.H assisted in the study design and contributed to acquisition, analysis, and interpretation of data and to critical revision of the manuscript. A.H. assisted in the study design; contributed to fieldwork management; and contributed to acquisition, analysis, and interpretation of data and to critical revision of the manuscript.

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REFERENCES

1. Homma T, Ueno T, Sekizawa K, Tanaka A, Hirata M. Interstitial pneumonia developed in a worker dealing with particles containing indium-tin oxide. *J Occup Health*. 2003;45(3):137-139.
2. Nakano M, Omae K, Tanaka A, et al. Causal relationship between indium compound inhalation and effects on the lungs. *J Occup Health*. 2009;51(6):513-521.
3. Nakano M, Omae K, Uchida K, et al. Five-year cohort study: emphysematous progression of indium-exposed workers. *Chest*. 2014;146(5):1166-1175.
4. Amata A, Chonan T, Omae K, Nodera H, Terada J, Tatsumi K. High levels of indium exposure relate to progressive emphysematous changes: a 9-year longitudinal surveillance of indium workers. *Thorax*. 2015;70(11):1040-1046.
5. National Toxicology Program. Toxicology and carcinogenesis studies of indium phosphide (CAS No. 22398-90-7) in F344/N rats and B6C3F1 mice (inhalation studies). *Natl Toxicol Program Tech Rep Ser*. 2001;499:7-340.
6. Nagano K, Nishizawa T, Umeda Y, et al. Inhalation carcinogenicity and chronic toxicity of indium-tin oxide in rats and mice. *J Occup Health*. 2011;53(3):175-187.
7. Ministry of Health, Labor, and Welfare. *Technical guideline for preventing health impairment of workers engaged in the indium tin oxide handling processes*. Tokyo, Japan: Government of Japan; 2010. <https://www.mhlw.go.jp/bunya/roudoukijun/anzeneisei42/dl/03.pdf>. Accessed 13 July, 2018.

8. Japan Society for Occupational Health. Recommendation of occupational exposure limits (2017–2018). *J Occup Health*. 2017;59(5):436–469.
9. IARC Working Group on the Evaluation of Carcinogenic Risk to Human. *Cobalt in hard metals and cobalt sulfate, gallium arsenide, indium phosphide and vanadium pentoxide*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 86. Lyon, France: International Agency for Research on Cancer; 2006:197–224.
10. Guha N, Loomis D, Guyton KZ, et al. Carcinogenicity of welding, molybdenum trioxide, and indium tin oxide. *Lancet Oncol*. 2017;18(5):581–582.
11. The American Conference of Governmental Industrial Hygienists. TLV®/BEI® guidelines, notice of intended changes list. 2018. <https://www.acgih.org/tlv-bei-guidelines/documentation-publications-and-data/notice-of-intended-changes/notice-of-intended-changes-list>. Accessed 13 July, 2018.
12. Hori M, Matsuda T, Shibata A, Katanoda K, Sobue T, Nishimoto H. Cancer incidence and incidence rates in Japan in 2009: a study of 32 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. *Jpn J Clin Oncol*. 2015;45(9):884–891.
13. Nogami H, Shimoda T, Shoji S, et al. Pulmonary disorders in indium-processing workers. *Nihon Kogyoku Gakkai Zasshi*. 2008; 46(1):60–64. (in Japanese).
14. Shiels MS, Chaturvedi AK, Katki HA, Gochoico BR, Caporaso NE, Engels EA. Circulating markers of interstitial lung disease and subsequent risk of lung cancer. *Cancer Epidemiol Biomarkers Prev*. 2011;20(10):2262–2272.
15. Afroz T, Hiraku Y, Ma N, et al. Nitrate DNA damage in cultured macrophages exposed to indium oxide. *J Occup Health*. 2018;60(2):148–155.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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