Health Effects of Toner Exposure Among Japanese Toner-Handling Workers: A 10-Year Prospective Cohort Study

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Abstract: The main objective of this study was to evaluate the risk of the respiratory diseases, i.e. pneumoconiosis, lung fibrosis, granulomatous pneumonitis, lung cancer and bronchial asthma, which have been reported as related to toner exposure. The second main objective was to clarify the association between toner exposure and parameters related with toner-handling worker’s health. We conducted a 10-year prospective cohort study from 2004 to 2013 in 296 Japanese toner-handling workers. The evaluation of toner exposure and medical health check were performed once a year. There was no obvious evidence of occurrence of lung diseases. We also investigated several health parameters to recognize the change of respiratory health before onset of pneumoconiosis, lung fibrosis, lung cancer and bronchial asthma. However there were some sporadic statistically significant findings, to bring all health parameters, we did not find obvious evidence that toner exposure would cause adverse health effects as a whole. We concluded that the possibility that toner exposure would cause adverse health effects was quite low.

Keywords: toner exposure, cohort study, biological effect evaluation.

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Introduction

The basic technology called xerography was established by Chester F. Carlson in 1938, and the first plain paper copy machine was released in 1959 in the United States. The progress of the digital technology in the late 1980s made computers and internet common in our modern society, and also advanced the digitization of office equipment. Since that time, there has been significant progress in the multi-functionalization of photocopiers and the personalization of laser printers. As a result, the use of photocopiers and laser printers has increased rapidly, and the amount of toner consumption has also increased significantly. A case report of siderosilicosis occurring in a 44-year-old woman who had worked in a photocopying shop for 6 years was published in Lancet in 1994 [1], while a case of granulomatous pneumonitis occurring in a 39-year-old man who had worked in a newspaper agency as a specialist in computer-based data collection for 18 months was...
also reported in Lancet 2 years later[1, 2]. In both case reports, the authors concluded that the pulmonary diseases developed from exposure to toner dust, although actual toner exposure was unclear in the reports.

In addition, carbon black, one of the components of toner particles, was re-classified by the International Agency for Research on Cancer (IARC) in 1996 as a Group 2B substance, meaning it is possibly carcinogenic to humans [3]. However, the carcinogenicity of carbon black has not been sufficiently demonstrated in humans[4–6], but only in experimental animals [7–9]. Concerns about the adverse health effects of toner grew rapidly in the late 1990s. A case of occupational asthma suspected to be caused by toner was reported in 2003 [10]. An epidemiological study with appropriate exposure assessment was needed to evaluate the health effect of toner at the workplace to prevent workers in toner production industries from health damage and to reassure users.

The main objective of this study was to evaluate the risk of respiratory diseases such as pneumoconiosis, lung fibrosis, granulomatous pneumonitis, lung cancer and bronchial asthma, reported as related to toner exposure, in toner-handling workers. We also surveyed several health parameters to ascertain any change in respiratory health before the onset of these diseases.

The second main objective was to clarify the association between toner exposure and these parameters related with toner-handling worker’s health.

**Subjects and Methods**

**Study design**

We conducted a 10-year prospective cohort study from 2004 to 2013 in Japanese toner-handling workers. To evaluate the risk of respiratory disease and to assess respiratory health associated with toner exposure, evaluation of toner exposure and medical health checks were performed once a year.

**Subjects**

The subjects were Japanese male employees in one plant aged from 24 to 51 in 2004. A total of 296 subjects were enrolled in the cohort. They consisted of toner-handling workers who handled toner routinely in their current work, and the referent workers were selected randomly from those other than the toner-handling workers, but of similar age distribution. Toner-handling work was composed of three major working categories: toner manufacturing, research and development (R&D) of toner, and engineering. All toner-handling workers were classified into one of these three categories, and individual work category was decided by their employment records. Subjects with unverified employment records were excluded from the analyses. The “toner manufacturing workers” basically handled toner in a fixed workshop that produces toner. The “R&D of toner workers” mainly worked either in the laboratory or office, and they usually handled toner in the draft chamber for the development of toner itself. The engineering workers handled toner to develop, evaluate, adjust and fix office equipment and did not appear to handle toner regularly. Only employees who had never handled toner since entering the company were sectioned off as the referent workers.

**Assessment of personal dust exposure level**

To evaluate the personal dust exposure measurement, we used a small dust sensor (Sibata personal dust sensor-2 (PDS-2), Sibata Scientific Technology Ltd.) for the measurement of personal dust exposure in the workers’ breathing zone. PDS-2 consists of two small parts, that is, sensor part with a light scattering photometer set at the collar or shoulder and a logger part at belt holding. Relative dust concentrations were logged at each minute as cpm (count/min.). In order to determine the mass concentration (mg/m³), parallel measurement with gravimetric method for respirable dust fraction were also needed with PDS-2. The parallel measurement for the light scattering photometers, such as PDS-2, is commonly conducted by means of a low volume-air-sampler (LV) or a high volume-air-sampler (HV). We used LV (sampling flowrate 20 lpm, NW354, Sibata scientific technology Ltd.) from 2004 to 2006 and then changed to HV (sampling flowrate 500 lpm, HV500F, Sibata scientific technology Ltd.) from 2007 to 2013 with size separator for respirable dust fraction. K factor ((mg/m³)/count/min. (cpm)) is determined as following:

\[ K = \frac{C}{C_{\text{photo}}} \]  

where C is concentration measured by gravimetric method (mg/m³), \( C_{\text{photo}} \) is relative concentration mea-
measured by PDS-2 (cpm).

The parallel samplings with LV or HV were conducted for 90 to 120 min. at typical points at the workplaces of the three categories, such as manufacturing, R&D and engineering.

Selected workers from three categories wore PDS-2 to sample air in the breathing zone during all work and rest operations. To avoid tobacco smoke, wearers were asked to record their lunch time and rest time.

The size distributions of dusts in the workplaces were also measured by an Andersen nonviable sampler (AN-200, Sibata scientific technology Ltd., Saitama, Japan) from 2005 to 2013. Dust particles were classified into 9 size fractions according to the 50% cut off aerodynamic diameter of each stage of the cascade impactor: stage 0 to stage 7 and back up filter; >11.0, 7.0–11.0, 4.7–7.0, 3.3–4.7, 2.1–3.3, 1.1–2.1, 0.65–1.1, 0.43–0.65 and < 0.43 μm.

**Medical health check**

To evaluate the risk of respiratory diseases, the incidence of pneumoconiosis, lung fibrosis, granulomatous pneumonitis, lung cancer and bronchial asthma was investigated every year by self-reported questionnaire. The responses were confirmed by the researchers and additional interviews were done if necessary. As parameters to recognize the change of respiratory health before onset of these diseases, biological markers in serum and urine, pulmonary function indices, chest X-rays (CXR) and subjective respiratory symptoms were examined once a year.

The following 8 biological markers in serum and 1 marker in urine were measured: c-reactive protein (CRP), immunoglobulin E (IgE), interleukin-4 (IL-4), interleukin-6 (IL-6), interleukin-8 (IL-8), interferon-γ (IFN-γ), sialylated carbohydrate antigen (Krebs von den Lungen-6, KL-6), and surfactant protein D (SP-D) in serum. 8-hydroxy-2'-deoxyguanosine (8-OHdG) in urine. For CRP, high sensitivity CRP (hs-CRP), which can detect low concentrations of CRP, was adopted from 2009. 8-OHdG levels in spot urine was known to vary greatly depending on individual physical activities and collecting time. The creatinine correction value (8-OHdG/Cre) was used for the analysis. These markers were selected by reviewing articles which describe the association between exposure to fine particle and reaction of biological markers synthetically [11–19].

The pulmonary function tests were performed with the pneumotachyo-type spirometry measuring unit Microspiro HI-701 and Microspiro HI-801 (Chest Corp., Tokyo, Japan) which met the standards stipulated by the American Thoracic Society (ATS) [20]. The pulmonary function tests were conducted three times for each subject to ensure validity and reproducibility of results. To adjust for differences in physical index and age, % vital capacity (%VC: VC × 100/predicted VC), percent forced expiratory volume in one second (%FEV1.0: FEV1.0 × 100/predicted FEV1.0), and percent FEV1.0 by forced vital capacity (FEV1.0%: FEV1.0 × 100/FVC) were used. Predicted VC and FEV1.0 were calculated by the formula described by the Clinical Pulmonary Functions Committee of the Japanese Respiratory Society in 2014 [21].

The chest X-ray examination was conducted always referring to the standard films [22] by two sets of medical doctors and recorded based on the International Labour Organization (ILO) international classification of radiographs of pneumoconiosis revised edition 2000 [23].

Subjective respiratory symptoms were obtained using a slightly modified version of a self-administered questionnaire standardized by American Thoracic Society (ATS) [24] and translated into Japanese. The researchers checked the replies and confirmed the details when needed. The following 4 symptoms were analyzed: chronic cough, chronic phlegm, chronic wheeze, and breathlessness. The symptoms are defined as below: chronic cough, presence of cough on most days (over 4 days a week) for 3 consecutive months or more during the last 1 year; chronic phlegm, presence of phlegm on most days (over 4 days a week) for 3 consecutive months or more during last 1 year; wheezing, presence of a wheezing sound over 2 times during the last 2 years; breathlessness or shortness of breath when hurrying on a level plane or walking up a slight hill.

**Analysis**

For the data to meet the assumption of homogeneity of variances, one-way analysis of variance (ANOVA) was conducted on continuous variables, and the Tukey's honestly significant difference (HSD) was used.
as the post-hoc test. For data that did not meet the assumption of homogeneity of variances, the Welch test was conducted on continuous variables and the Games Howell test was used as the post-hoc test. The Pearson’s chi-square test was conducted on categorical variables, complemented by the adjusted residual analysis. Multiple regression analysis was conducted to estimate the effects of the current toner exposure status and the cumulative toner exposure on health parameters. All statistical analyses were carried out using SPSS 22.0J (IBM SPSS Inc.).

Ethical approval

All study participants provided informed consent, and this study was reviewed and approved by the Human Ethics Committee for Epidemiological Research at the University of Occupational and Environmental Health, Japan.

Results

Subjects

One of the 296 enrolled subjects did not participate in the survey and we were able to follow 192 subjects until 2013 (follow up rate: 65.1% (192/295)). After excluding 4 subjects from the analysis because of unverified working history, there were a total of 291 subjects, consisting of 155 toner-handling workers in the following breakdown: 36 toner manufacturing workers, 30 research and development (R&D) of toner workers, 89 engineering workers, and 136 referent workers at the start of the survey in 2004. In 2013, the remaining 190 subjects were composed of 112 toner-handling workers in the following breakdown: 26 toner manufacturing workers, 20 R&D of toner workers, 66 engineering workers, and 78 referent workers. Table 1 describes the demographic of the subjects in 2004. There was a significant difference in age by one-way ANOVA ($P < 0.01$) and the Turkey’s HSD suggested that toner manufacturing workers (39.1 ± 6.2 years) were significantly older than the R&D of toner workers (34.7 ± 5.6 years, $P < 0.01$) and the engineering workers (36.0 ± 5.2 years, $P = 0.02$). Statistically significant differences were not found in cumulative toner-handling years and smoking status.

Evaluation of toner exposure

Figure 1 shows the K factor for each category. The parallel measurements for K factors were conducted 8 times, 5 times and 6 times in toner manufacturing, R&D of toner and engineering workplaces, respectively, from 2004 to 2013. In 2009 and 2010, K factors of parallel measurement were not conducted in any workplaces. The measurements were conducted near the toner handling locations as the representative values, because the workers moved from floor to floor or room

Table 1. The demographics of the subjects in 2004

| variables                      | Toner-handling | Toner manufacturing | R&D of toner | Engineering | Referent | $P$-value |
|--------------------------------|----------------|---------------------|--------------|-------------|----------|-----------|
| Subjects                       | n              | 155                 | 36           | 30          | 89       | 136       |
| Age years (SD)                 | 36.5 (5.7)     | 39.1 (6.2)          | 34.7 (5.6)   | 36.0 (5.2)  | 37.6 (5.6) | <0.01*    |
| Cumulative toner-handling years till 2003 | 8.6 (6.1)      | 9.8 (5.7)           | 7.8 (6.9)    | 8.4 (6.0)   |          | 0.37      |
| Period to start handling toner |                |                     |              |             |          |           |
| before 1993 n (%)              | 74 (47.7)      | 20 (55.6)           | 10 (33.3)    | 44 (49.4)   |          |           |
| 1994–2003 n (%)                | 70 (45.2)      | 12 (33.3)           | 19 (63.3)    | 39 (43.8)   |          | 0.16      |
| from 2004 on n (%)             | 11 (7.1)       | 4 (11.1)            | 1 (3.3)      | 6 (6.7)     |          |           |
| Smoking status                 |                |                     |              |             |          |           |
| non-smoker n (%)               | 64 (41.3)      | 13 (36.1)           | 12 (40.0)    | 39 (43.8)   | 63 (46.3) |           |
| current smoker n (%)           | 65 (41.9)      | 18 (50.0)           | 16 (53.3)    | 31 (34.8)   | 54 (39.7) | 0.30      |
| ever smoker n (%)              | 26 (16.8)      | 5 (13.9)            | 2 (6.7)      | 19 (21.3)   | 19 (14.0) |           |

*: statistically significant ($P < 0.01$) by one-way analysis of variance (ANOVA) and the Turkey’s HSD. R&D: research and development
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3.3–4.7 or 4.7–7.0 μm, as shown in asterisk. The peak sizes of the dusts are similar to the size of the toner particles.

To evaluate the personal dust exposure measurement, we used a small dust sensor at workers’ breathing zone. Time averaged exposure concentration for each worker was calculated by 10-year average K factor for each category. Dust concentration was measured 8 times, 5 times and 6 times in each workplace in 10 years. The mean, median, minimum (min.), and maximum (max.) values are described as mg/m³.

R&D: research and development, n.d.: no data
The smaller size fractions (<1.1 \( \mu \)m) should be derived from other sources, such as the data of 2013.

**Health outcomes**

**Incidence of lung diseases**

In our 10-year observation, there were no cases of pneumoconiosis, lung fibrosis, granulomatous pneumonitis, or lung cancer. Of the 291 subjects, there were 24 workers who reported present and past history of bronchial asthma in 2004. Of the 24 subjects, 7 subjects reported completely quiescent childhood asthma. Since childhood asthma was distinguished as different from adult asthma, the remaining 17 subjects, i.e., 1 R&D of toner worker, 7 engineering workers and 9 referent workers, were excluded from the analysis. During the study period, 1 engineering worker and 4 referent workers reported incidences of bronchial asthma. There were no subjects in the toner manufacturing workers and R&D of toner workers. The cumulative incidence rate was 6.8 /1,000 persons in the whole toner-handling workers, 12.2 /1,000 persons in the engineering workers and 31.5 /1,000 persons in the referent workers. The risk ratios compared to the referent workers were 0.22 (95% confidence interval (95%CI: 0.17–0.27) in the toner-handling workers, 0.39 (95%CI: 0.29–0.51) in the engineering workers.

**Measurement of health parameters**

**Baseline analysis**

Table 4 shows the comparison of the biological markers, the pulmonary function indices and the prevalence of subjective respiratory symptoms between each working category and the referent workers, in 2004. Among measured biological markers, IL-4, IL-8 and IFN-\( \gamma \) were excluded from the analysis because these 3 biological markers were not detected in over 90% of the

| Size range (\( \mu \)m) | Toner manufacturing | R&D of toner | Engineering |
|-------------------------|---------------------|--------------|-------------|
|                         | 2005  | 2006  | 2008-1 | 2008-2 | 2009  | 2010  | 2011-1 | 2011-2 | 2012-1 | 2012-2 | 2013-1 | 2013-2 | 2007-1 | 2007-2 |
| back up filter          | –     | –     | 1.4    | 5.6    | 2.6    | 3.9    | 0.8    | 4.4    | 2.4    | 8.1    | 2.7    | 47.9*  | 2.4    | 3.2    |
| 0.43–0.65               | 3.4   | 4.8   | 1.4    | 5.1    | 0.7    | 3.4    | 0.9    | 3.9    | 3.3    | 10.5   | 3.5    | 6.9    | 1.7    | 2.5    |
| 0.65–1.1                | 5.6   | 8.5   | 1.5    | 7.4    | 3.4    | 2.9    | 1.4    | 3.5    | 3.5    | 9.0    | 4.3    | 2.8    | 1.4    | 2.4    |
| 1.1–2.1                 | 6.3   | 4.8   | 1.6    | 5.6    | 3.4    | 3.4    | 3.9    | 2.4    | 4.7    | 3.1    | 1.8    |        |        |
| 2.1–3.3                 | 12.7  | 7.6   | 11.3   | 7.2    | 6.8    | 10.4   | 15.3   | 9.5    | 5.2    | 7.3    | 9.4    | 6.5    |        |        |
| 3.3–4.7                 | 24.5* | 19.2  | 34.8*  | 12.7   | 18.0   | 24.3   | 31.4*  | 24.0   | 13.6   | 16.4   | 25.9   | 7.4    |        |        |
| 4.7–7.0                 | 22.1  | 29.4* | 29.2   | 22.1*  | 31.1*  | 28.1*  | 31.4*  | 25.9*  | 18.5   | 19.6*  | 29.3*  | 10.1   |        |        |
| 7.0–11                  | 10.6  | 15.8  | 11.3   | 12.7   | 19.6   | 13.8   | 8.2    | 13.9   | 17.9   | 12.4   | 13.4   | 6.5    |        |        |
| >11                     | 14.8  | 9.9   | 7.4    | 21.7   | 14.5   | 9.8    | 7.1    | 11.0   | 33.3*  | 12.0   | 8.4    | 10.1   |        |        |

In the most cases of toner manufacturing and engineering workplaces, the peak sizes of the dusts are 3.3–4.7 \( \mu \)m or 4.7–7.0 \( \mu \)m and similar to the size of the toner particles. The smaller size fractions (<1.1 \( \mu \)m) should be derived from other sources. R&D: research and development, *: Maximum ratio (%) in the Andersen sampler stages.
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subjects. Although most of the parameters did not show significant differences, there was a statistically significant difference determined by the one-way ANOVA in forced expiratory vol. 1.0 (FEV$_{1.0}$)\% ($P = 0.01$). The Tukey's HSD revealed that FEV$_{1.0}$\% was statistically significantly lower in the referent workers (84.4±5.4%) compared to the engineering workers (86.6±5.7%).

**Longitudinal analysis**

**Biological markers in serum and urine**

The association of the dust exposure levels and each biological marker was shown on a semilogarithmic graph (Fig. 2). There was no evidence that the higher level dust exposure caused the high biological marker level in this study.

**Pulmonary function tests**

Pulmonary function is known to decrease with age [26], and it is also known that pulmonary function of smokers would decrease much more than that of non-smokers [27, 28]. Based on the hypothesis that pulmonary function of the toner-handling workers would decrease much more than the referent workers if toner causes lung disorder the same as tobacco, to assess the effect of toner exposure, the annual change of the pulmonary function indices were used. To get the annual change, the individual slope of vital capacity (VC), forced vital capacity (FVC) and FEV$_{1.0}$ were calculated. Multiple regression analysis was conducted using the annual change of the pulmonary function indices as the dependent variables and the estimated mean dust concentration of 10 years and the cumulative toner-handling years till 2013 as the independent variables adjusting for age and smoking status at 2004. There were no significant effects of the estimated mean dust concentration and the cumulative toner-handling years (Table 5).

Table 4. The comparison of the biological markers, the pulmonary function indices and the prevalence of subjective respiratory symptoms between each working category and the referent workers, in 2004

| Workplace       | Toner manufacturing | R&D of toner | Engineering | Referent | P-value |
|-----------------|---------------------|--------------|-------------|----------|---------|
| Subjects (n)    | 36                  | 30           | 89          | 136      |         |
| Biological markers: value (SD) |                     |              |             |          |         |
| CRP (mg/dl)     | 0.13 (0.15)         | 0.11 (0.03)  | 0.13 (0.12) | 0.13 (0.11) | 0.75   |
| IgE (IU/ml)     | 108.1 (127.5)       | 172.8 (188.6)| 162.1 (258.1)| 203.4 (331.5) | 0.06   |
| IL-6 (pg/ml)    | 0.55 (0.42)         | 2.12 (5.74)  | 0.63 (0.90) | 0.81 (1.16) | 0.13   |
| KL-6 (U/ml)     | 202.9 (68.8)        | 197.3 (46.4) | 208.6 (64.7)| 215.9 (66.0)| 0.43   |
| SP-D (ng/ml)    | 53.6 (20.7)         | 64.2 (24.3)  | 51.3 (27.5) | 53.2 (28.2) | 0.16   |
| 8-OHdG/Cre (ng/mg) | 4.60 (1.76)        | 4.61 (1.48)  | 4.90 (1.67) | 4.52 (1.83) | 0.45   |
| Pulmonary function indices: value (SD) |                     |              |             |          |         |
| VC (l)          | 4.5 (0.6)           | 4.6 (0.6)    | 4.6 (0.6)   | 4.6 (0.6)  | 0.83   |
| %VC (%)         | 100.6 (9.6)         | 98.9 (11.8)  | 98.8 (12.1) | 100.7 (10.1) | 0.56   |
| FVC (l)         | 4.3 (0.5)           | 4.5 (0.6)    | 4.5 (0.7)   | 4.4 (0.6)  | 0.46   |
| FEV$_{1.0}$ (l) | 3.6 (0.5)           | 3.8 (0.5)    | 3.9 (0.6)   | 3.7 (0.5)  | 0.11   |
| %FEV$_{1.0}$ (%)| 100.3 (10.3)        | 98.4 (13.6)  | 102.6 (12.6)| 101.1 (9.2) | 0.45   |
| FEV$_{1.0}$\% (%)| 84.4 (5.2)          | 83.8 (6.0)   | 86.6 (5.7)  | 84.4 (5.4) | 0.01*  |
| Prevalence of subjective respiratory symptoms |                     |              |             |          |         |
| Chronic cough (%)| 0.0                 | 6.7          | 4.5         | 3.7       | 0.53   |
| Chronic phlegm (%)| 13.9                | 3.3          | 5.6         | 5.1       | 0.22   |
| Chronic wheezing (%)| 2.8                 | 3.3          | 3.4         | 2.9       | 1.00   |
| Breathlessness (%)| 13.9                | 3.3          | 2.2         | 6.6       | 0.08   |

CRP: c-reactive protein, IgE: immunoglobulin E, IL-6: interleukin-6, KL-6: sialylated carbohydrate antigen (Krebs von den Lungen-6), SP-D: surfactant protein D, 8-OHdG: 8-hydroxy-2’-deoxyguanosine, VC: vital capacity, %VC: percent vital capacity, FVC: forced vital capacity, FEV$_{1.0}$: forced expiratory volume in one second, %FEV$_{1.0}$: percent forced expiratory volume in one second, FEV$_{1.0}$\%: percent FEV$_{1.0}$ by forced vital capacity. *: statistically significant ($P < 0.05$) by the one-way ANOVA
**Fig. 2. Dust exposure levels and biological markers in serum and urine of workers.** The abscissa denotes the dust exposure level (mg/m³), and the ordinate the mean of biomarker. There was no evidence that the high level dust exposure caused the high biological marker level. A: c-reactive protein (CRP), B: hyper sensitive c-reactive protein (hs-CRP) in serum, C: immunoglobulin E (IgE), D: interleukin-6 (IL-6) in serum, E: sialylated carbohydrate antigen (Krebs von den Lungen-6: KL-6) in serum, F: surfactant protein D (SP-D) in serum, and G: 8-hydroxy-2'-deoxyguanosine (8-OHdG)/cre in urine.
Table 5. Multiple regression analysis in relation with the annual change of the pulmonary function indices

| Pulmonary function indices | VC (ml/year) | FVC (ml/year) | FEV_{1.0} (ml/year) |
|---------------------------|------------|---------------|---------------------|
| Independent variables     | B          | 95% C.I.      | P-value             | B          | 95% C.I.      | P-value             | B          | 95% C.I.      | P-value             |
| Estimated mean dust concen-| -1.19      | -2.84 - 0.45  | 0.15                | -1.14      | -2.71 - 0.43  | 0.15                | -0.44      | -1.91 - 1.03  | 0.56                |
| tration of 10 years confounders |
| Age 1 year                | 0.82       | -1.81 - 0.17  | 0.10                | 0.26       | -0.69 - 1.20  | 0.60                | 0.32       | -0.56 - 1.20  | 0.47                |
| Smoking status current smoker | 5.35       | -6.70 - 17.39 | 0.38                | 7.36       | -4.14 - 18.85 | 0.21                | -2.14      | -12.88 - 8.60 | 0.70                |
| ever smoker               | 20.68      | 4.10 - 37.26  | 0.02*               | 4.26       | -11.57 - 20.08 | 0.60                | 13.86      | -0.93 - 28.63 | 0.07                |
| non-smoker                |            |               |                     |            |               |                     |            |               |                     |
| Cumulative toner-handling years till 2013 confounders 1 year | -0.34      | -0.93 - 0.24  | 0.25                | -0.37      | -0.93 - 0.19  | 0.19                | -0.19      | -0.71 - 0.33  | 0.48                |
| Age 1 year                | 0.72       | -1.70 - 0.27  | 0.15                | 0.36       | -0.58 - 1.30  | 0.45                | 0.36       | -0.51 - 1.24  | 0.41                |
| Smoking status current smoker | 5.31       | -6.77 - 17.39 | 0.39                | 7.40       | -4.12 - 18.92 | 0.21                | -2.03      | -12.78 - 8.72 | 0.71                |
| ever smoker               | 20.06      | 3.50 - 36.62  | 0.02*               | 3.71       | -12.08 - 19.50 | 0.64                | 13.70      | -1.04 - 28.43 | 0.07                |
| non-smoker                |            |               |                     |            |               |                     |            |               |                     |

Multiple regression analysis was conducted using the annual change of the pulmonary function indices as the dependent variables and the estimated mean dust concentration of 10 years and the cumulative toner-handling years till 2013 as the independent variables adjusting for age and smoking status at 2004. VC: vital capacity, FVC: forced vital capacity, FEV_{1.0}: forced expiratory volume in one second, B: regression coefficient, C.I.: confidence interval, *: statistically significant (P < 0.05)

Chest x-ray examination
A total of 2,429 CXR films were interpreted by two sets of medical doctors and recorded based on the ILO international classification of radiographs of pneumoconiosis revised edition 2000 [23]. However, there were no subjects with obvious fibroproliferative changes suspected to pneumoconiosis, 18 films were classified into 0/1 category representing mildest fibrotic change in 10 years observation. The prevalence of 0/1 category was 0.61% (2/329) in the toner manufacturing workers, 1.28% (3/234) in the R&D of toner workers, 0.38% (3/784) in the engineering workers and 0.92% (10/1082) in the referent workers (Table 6). The relative risk of the prevalence of 0/1 category compared to the referent workers was 0.94 (95% CI: 0.21 - 4.26) in the toner manufacturing workers, 1.70 (95% CI: 0.45 - 6.03) in the R&D of toner workers, and 0.57 (95% CI: 0.16 - 2.10) in the engineering workers, and none of the relative risks were significant.

Subjective respiratory symptoms
To estimate the effect of the dust exposure level and the cumulative toner-handling years till 2013 on subjective respiratory symptoms, logistic regression analyses using generalized estimating equations (GEE) which were the statistical model for repeated measured data [28] were conducted. Table 7 shows the results of the generalized estimating equations on the subjective respiratory symptoms. There were no estimated statistically significant effects of the dust exposure levels and the cumulative toner-handling years till 2013 adjusting for age and smoking status. On the other hand, the significant effects of current smoking status to increase chronic phlegm, chronic wheezing and breathlessness, and the effect of age to chronic wheezing and breathlessness were observed.

Discussion
We conducted a 10-year prospective cohort study on Japanese workers and there was no obvious evidence of the occurrence of lung diseases. We also investigated several health parameters to demonstrate the change of respiratory health before onset of pneumoconiosis, lung fibrosis, lung cancer and bronchial asthma. However there were some sporadic statistically significant findings, to bring all health parameters, we did not find obvious evidence that toner exposure would cause the adverse health effects as a whole.

The strength of this study lies in our detailed assessment of personal toner exposure. In the previous case reports, there was no information of exposure status, i.e. they only described the rough workplaces and working duration [1, 2].
The other strength lies in the analysis considering the effect of the cumulative toner-handling years confirmed retrospectively. There were 38 subjects who engaged in toner-handling work over 20 years (maximum=30). Although the detailed personal dust exposure measurement were not conducted before 2003, the toner dust exposure levels before 2003 were guessed to be equal or greater than that after 2004, and in view of the progress of the personal productive equipment and the forced management of the safety and health. It is a valuable finding that there were no obvious occurrences of lung diseases related to toner in the subjects with over a 20-year exposure. Although various types of dusts are known to cause lung fibrotic change when
inhaled in the lung, toner particle is considered less likely to cause lung fibrosis. The possibility of toner exposure to develop lung cancer seemed to be low.

The subjects were users of photocopiers in the previous case reports [1–3]. Usually, users of photocopiers do not deal with toner directly, because toner is completely packed in the cartridges and the users only replace the cartridge when toner runs out. Our subjects were employees of a toner manufacturing company. Despite the differences in the amount, the subjects surely handled toner. It is clear that toner exposure was higher in the toner manufactures than in the users, and it is worth conducting this study in higher exposed subjects.

In this study, the dust exposure levels of the workers were quite low. Considering that the toner manufacturing workers usually used the respiratory protective equipment and the R&D of toner workers usually handled toner in the fume cupboards, the actual toner exposure levels may have been much smaller. In either case, the amount of exposed toner was estimated small enough to not cause adverse health effects.

Serum sialylated carbohydrate antigen Krebs von den Lungen-6 (KL-6) is known as the marker to reflect the severity and activity of lung injury [16], and several studies reported the elevation of KL-6 in especially interstitial lung diseases (ILDs) such as interstitial pneumonia, idiopathic pulmonary fibrosis (IPF), hypersensitivity pneumonitis and several other diseases, and inhalation of irritants, e.g. asbestos, silica, talc, coal dust, at work was known as a cause of the interstitial lung diseases. As the item of the special health examination for the workers who handled the indium, especially its compound (indium tin oxide (ITO)), was found to cause interstitial pneumonia with the lung fibrosis, KL-6 was adopted from 2013 in Japan. KL-6 was considered to be useful to detect lung fibrosis in the early stages [29, 30]. Kobayashi et al described the cut off value of KL-6 for interstitial pneumonia as 500 U/ml (sensitivity: 85%, specificity: 98%) by the receiver operator characteristic curve using the data of 273 healthy volunteers and 77 interstitial pneumonia patients, and there were no subjects whose individual mean of KL-6 was greater than the cut off value [31]. Together with the result of KL-6, the pulmonary function tests and the CXR examination, we determined that inhaled toner dust as low concentration as our study would not cause the lung fibrosis even if exposed over 10 years.

As a chest image inspection, only the CXR was conducted in our study. Although the international standard inspection of pneumoconiosis was the CXR, the chest computed tomography (CT) had become of greater use for the clinical diagnosis of pneumoconiosis recently. Several reports suggested that the chest CT was more effective than the CXR for lung cancer screening [32, 33]. The obtained information would be more valuable if the chest CT was conducted.

There were limitations in our study. First, the follow-up rate over 10 years decreased to 65.1%. Although 246 subjects participated in the study till 2012, 54 subjects dropped out before the last survey due to not health problems but the staff arrangement with re-organization. That was something we could not help because of the decision of the company. Secondly, although our study focused on the respiratory health effect of toner exposure, there was some epidemiological study that described the association of fine particle with cardiovascular diseases [34–36]. To assess the total health effects of toner exposure, cardiovascular diseases might have to be set as the endpoints.

When we started this cohort study, the health adverse effect of toner particles was a concern. In these 10 years, concern about the health impairment due to nanoparticles emitted from laser printers increased [37]. However we clarified the health effect of toner particle itself in this report, and it is therefore inappropriate to apply this result to emitted nanoparticles. To prove the health effect related to substances emitted from laser printers and/or toner particle clearly, new epidemiological studies are necessary for appropriate assessment.

In conclusion, we could not find any obvious risk of toner exposure to cause respiratory diseases and the possibility that toner exposure can cause adverse health effects is considered to be quite low.

Conflict of interest

A company of toner-handling workers paid the cost for this study to the University of Occupational and Environmental Health, Japan (UOEH) as a consideration. Therefore, to avoid a bias for results, this study was carried out under a guideline of the Japan Business Machine and Information System Industries As-
sociation (JBMIA). The fairness of this study has been secured by contract between the company and UOEH.

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我が国のトナー製造従事者におけるトナー曝露の生体影響: 10年の前向きコホート研究

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要   旨: 本研究の主な目的は、トナー製造従事者におけるじん肺症、肺線維症、肉芽腫性肺炎、肺がん、喘息などの呼吸器疾患のリスクを評価することである。第二の目的は、トナー粒子曝露と生体指標との間の関係について明らかにすることである。我々は2004年から2013年の間に日本におけるトナー製造従事者296名に対し10年間の前向きコホート研究を行った。トナー粒子曝露と健診結果の評価は各年ごとに行った。明らかな肺疾患発生は認められなかった。我々はまたじん肺、肺線維症、肺がんや喘息の発症に関連する呼吸器系要因についてもスパイロメーターや質問票による調査を行った。しかしながら散発的な統計的所見は認めるもの、トナー曝露が総じて有害な生体影響を起こすという明らかな証拠は得られなかった。結論として、トナー粒子曝露が生体影響を起こす可能性は極めて低い。

キーワード: トナー曝露、コホート研究、生体影響評価。

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