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# A Cohort Study on Respiratory Symptoms and Diseases Caused by Toner-Handling Work: Longitudinal Analyses from 2003 to 2013

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**Abstract:** The purpose of this study was to examine the effects of toner-handling work on respiratory symptoms and diseases. We conducted a prospective cohort study of 1468 workers between 2003 and 2013. The cohort included 887 toner-handling workers and 581 non-toner-handling workers, employed in one toner and copier manufacturing enterprise. Toner-handling workers were subdivided into two groups based on the 8-h time-weighted average toner exposure concentration for each work category in the baseline survey. We compared the incidence of respiratory disease and longitudinal changes in the prevalence of subjective respiratory symptoms among three groups, as follows: High-concentration toner exposure group, the low-concentration toner exposure group, and a control group. The incidence of respiratory disease and changes in the prevalence of subjective respiratory symptoms were not significantly different between the non-toner-handling group and the toner-handling group. In contrast, the odds ratio for yearly changes in the prevalence of wheezing without asthmatic response was significantly lower in the high-concentration toner exposure group than in the control group. At the study site, dust scattering was well controlled and workers used respiratory protection appropriately. These findings suggest that toner-handling work had little adverse effect on respiratory function in a work environment with sufficiently controlled ventilation.

**Keywords:** workplace air environment; occupational health; respiratory effects; toner dust; printer; cohort study

## 1. Introduction

Toner is a powder mixture comprising particles ranging in size from 5 to 10 μm in diameter, used for laser printing, and contains colorants such as carbon black in resin particles. It also contains nanoparticles such as titanium dioxide and amorphous silica, which adhere to the surface of toner particles as external additives.

The health effects of particulate matter (PM) have been extensively studied with regard to air pollution and health effects. Since PM is mainly taken into the body by inhalation, the respiratory system is easily affected. One epidemiological study on the respiratory effects of non-occupational exposure to air pollutants reported that the prevalence of asthma and the frequency of sensitization to aeroallergens were higher in urban areas than in rural areas [1]. Studies on occupational exposure to air pollutants reported that traffic policemen who were exposed to motor vehicle-generated air pollutants, including diesel exhaust particles, for a long period showed a significant decline in respiratory function [2,3]. A systematic review of studies on the health effects of occupational and non-occupational exposure to air pollutants also reported that occupational exposure to air pollution increased the risk of allergic and pulmonary disease [4]. Epidemiological studies to date suggest that exposure to PM induces lung injury and inflammation, promotes airway hyperresponsiveness, and exacerbates asthma.

With regard to the health effects of toner, in 1994 the first case of siderosilicosis was reported as a toner-induced health effect [5]. This was followed by case reports on sarcoidosis, allergic rhinitis, and asthma [6–8]. These reports raised concerns about the health effects associated with toners and copy printers. Recent studies have suggested that printers may generate and emit fine particles when in use [9–11], suggesting the potential health effects of toners and toner-based printing. However, because the diameter of particles emitted during printing is mostly in the submicron range, it is unlikely that these particles are toner dust itself. The health effects of exposure to fine particles from printers and toner dust must, therefore, be separately assessed.

Several epidemiological studies have assessed the health effects of toner dust exposure in workers at toner manufacturing factories [12–15], and suggest the potential adverse effects of inhaling toner dust. However, these previous studies were limited due to sample size, study design, and other factors. Furthermore, there is insufficient scientific evidence to assess the extent of the effect of toner dust exposure on the respiratory system. There is a need for well-designed longitudinal research in this area.

Starting in 2003, we conducted a 10-year cohort study of employees of a Japanese toner and copy machine manufacturing enterprise. The objective of this study was to determine the health effects of toner-handling work on the prevalence of subjective respiratory symptoms and the onset of respiratory diseases (granulomatous interstitial pneumonia, pneumoconiosis, lung cancer, bronchial asthma) across a 10-year period.

## 2. Materials and Methods

### 2.1. Study Design and Settings

This was a prospective cohort study conducted across a consecutive 10-year period. A baseline survey was conducted in 2003, and follow-up surveys were implemented every year from 2004 (1st survey) to 2013 (10th survey). Each participant underwent an annual health check and completed (1) a toner-handling work status survey; (2) a questionnaire-based survey on self-reported respiratory symptoms, diseases; (3) chest radiography; (4) a pulmonary function test; and (5) blood and urine biomarker tests. In this study, we examined the relationship between toner-handling work and findings from the questionnaire.

### 2.2. Participants

A total of 918 male workers aged 19 to 50 years as of April 2003, who were engaged in toner-handling work at one toner and copy machine manufacturing enterprise in Japan, were eligible for this study (toner-handling group). Toner-handling work was classified into 5 categories, as follows: Toner development, toner manufacturing, toner or copy machine development, toner or copy machine recycling, and customer service. In addition, 586 workers were enrolled as controls (non-toner-handling group). To control for potential biases arising from differences in lifestyle and nutritional status due to socio-economic factors, differences in non-occupational exposure to air pollution due to living conditions and environmental factors, and differences in occupational exposure to air pollution other than toner, subjects in the non-toner-handling group were recruited from among male workers of a similar age working at the same business sites as those of the toner-handling group. Non-toner-handling workers engaged mainly in deskwork and had never engaged in toner-handling work; their major duties did not involve copy printing. According to Cohen, assuming a power of 80%, a significance of 5%, and a small effect size, a total of 785 subjects would be required to perform a chi-squared test with 1 degree of freedom [16]. Therefore, at least 393 samples were required for each group to detect small differences between the toner-handling and non-toner-handling groups.

### *2.3. Self-Administered Questionnaire*

We collected information on participants' occupational history, history of illness, current illness, and respiratory symptoms using the Japanese translation of the standardized self-administered questionnaire by the American Thoracic Society (ATS-DLD-78A) [17]. However, we made the following modifications to the original Japanese version questionnaire: We deleted questions concerning family history, school history, and living environment, and added questions on the history of present illness due to allergic diseases, handling of organic solvents, handling of dust other than toner, and toner-handling work. The following five chronic symptoms were assessed: Chronic cough, defined as a cough that persisted every day for 3 months or more within a year; chronic phlegm, defined as phlegm that persisted every day for 3 months or more within a year; chronic cough and phlegm, defined as cough and phlegm that persisted with higher severity than usual for 3 weeks or more; wheezing without asthmatic response that occurred twice or more nearly within a year; and shortness of breath when the subject walked fast on a flat road or up a gentle slope.

### *2.4. Toner Particle*

In this toner and copy machine manufacturing enterprise, conventional toner (C-toner), which is made by pulverizing raw materials, and emulsion aggregation toner (EA-toner) were manufactured. Production of EA-toner was lower than that of C-toner between 2004 to 2006, but became higher in 2007 and continued to increase thereafter. The survey was conducted among toner-handling workers who worked in environments with a mixture of C-toner and EA-toner production.

The average particle diameters of C-toner and EA-toner manufactured by this enterprise were 6.5 μm and 5.8 μm. The components of C-toner (black) included 70–80% polyester resin, 10−20% ferrite powder (iron oxide, manganese oxide), <10% amorphous silica, <10% carbon black, and <1% titanium dioxide. Those of EA-toner (black) included 60–70% styrene-acrylate resin, 10–20% ferrite powder (iron oxide, manganese oxide), <10% polyethylene, <10% amorphous silica, <10% carbon black, and <1% titanium dioxide [18,19].

### *2.5. Toner Exposure Assessments*

We have previously reported on the detailed assessment of toner exposure [19–22]. In this study, every year between 2003 and 2010, several subjects randomly selected from among workers engaged in five work categories had their toner exposure measured using a personal dust sampler. We conducted personal exposure measurements based on the Working Environment Measurement Standards [23]. In the survey from 2003 to 2004, a Filter Holder of Personal Total and Respirable Dust Sampler (Model PS-43, Roken type, Sibata Scientific Technology, Ltd., Soka, Saitama, Japan) with glass fiber filters (polytetrafluoroethylene (PTFE) binding, T60A20 type φ25 mm, Tokyo Dylec Corp., Tokyo 601-8027, Japan) and an AirChek 2000 Sample Pump (SKC Inc., Eighty Four, PA 15330, USA) or Gilian GilAir-5 Air Sampling Pumps (Sensidyne, St. Petersburg, FL 33716, USA) were used with a flow rate of 1.5 L/min. Toner-handling workers wore a data recorder on the left hip and a detector around their neck. Measurement was continued from the beginning of the workday until the end. In 2005, part of the Working Environment Measurement Standards was revised in Japan, and the definition of respirable dust was revised from equal to or less than 7 μm to 4.5 μm. In accordance with this revision, the personal dust sampler was changed to a Filter Holder for Personal Dust Sampler (Model NWPS-254, Sibata Scientific Technology Ltd., Soka, Saitama 340-0005, Japan) in the survey after 2005. The filter and air sampling pump were the same as in 2004, and the flow rate was 2.5 L/min. Respirable dust trapped in the filter was measured with an electric balance, and the measured quantity was divided by the total aspirated air volume to calculate the respirable dust concentration. The 8-hour time-weighted average (TWA8h) was calculated by the formula indicated by the American Conference of Governmental Industrial Hygienists (ACGIH) [24], using the respirable dust concentration and working time. We calculated the mean TWA8h values in each work category.

### *2.6. Analysis of Diseases Chosen as Endpoints*

Considering the respiratory effects of PM, if the toner dust has an effect on human health, it was expected that toner inhaled into the bronchi or bronchioles would cause a protective response in the body which, if severe, would cause inflammation and tissue destruction followed by tissue fibrosis due to repair mechanisms. Based on these hypotheses and previous case reports possibly related to toner exposure [5–8], we chose Granulomatous interstitial pneumonia, pneumoconiosis, lung cancer, and bronchial asthma as endpoints. The incidence of these diseases was compared between the toner-handling group and the non-toner-handling group. When subjects indicated a new onset of a disease in the questionnaire, the follow-up was discontinued in the corresponding survey year. When subjects did not provide a response regarding disease onset in any given year, follow-up was ended in that survey year. The length of the observation period in one year was indicated as 0.5 year in both subjects who discontinued and those who had a new onset of a disease. Bronchial asthma is known to have a wide variety of clinical courses, including childhood-onset asthma with chronic symptoms, childhood-onset asthma with remission followed by adulthood recurrence, and adulthood-onset asthma, making it difficult to determine asthma-related incidence. The odds ratio for asthma prevalence before and after each 1-year survey period was compared between the toner-handling group and the non-toner-handling group to determine the effect of toner exposure on yearly changes of the prevalence of asthma.

### *2.7. Analysis of Subjective Respiratory Symptoms*

In the analysis of panel data by survey year, a chi-squared test and Fisher's exact test were performed for qualitative variables, and a simple *t*-test and Welch's *t*-test were performed for quantitative variables. A logistic regression analysis using a generalized estimating equation (GEE), with each participant as the subject variable and the survey year as the within-subject variable, was applied to the longitudinal data [25]. To adjust for the effects of potential confounding factors, data were analyzed using three models with additional variables. In Model 1, which did not adjust for any confounding factors, the respiratory symptoms served as the dependent variable, toner-handling work served as the independent variable, and the survey year served as the covariate. In Model 2, data were adjusted for baseline age and body mass index (BMI). In Model 3, data were further adjusted for smoking, asthma, allergic rhinitis, allergic dermatitis, pneumonia, sinusitis, dust other than toner work, and organic solvent work. Since a positive independent relationship between lung function impairment and abdominal obesity is well known [26], we adopted BMI as a confounding factor. As for other confounding factors we adopted, these were expected to affect the prevalence of respiratory symptoms based on published baseline studies [27,28] and interim reports [20–22]. In the analysis for the symptom wheezing without asthmatic response, only asthma was excluded as a confounding factor. The corrected quasi-likelihood under the independence model criterion (QICC) was used to select models with the highest fit. Furthermore, Model 4, which adjusted for a combination of the confounding factors of the models with the highest fit, was used to analyze differences among variant toner exposure concentration levels. If any significant effect of toner exposure on each respiratory symptom was observed, we also performed GEE analysis adjusted with the same confounding factor as Model 4 separately for each exposure concentration level to determine the odds ratio for yearly changes in each group.

The effect of toner exposure was identified by the value obtained by dividing the odds ratio for "respiratory symptoms" before and after a 1-year survey period in the toner-handling group (referred to as the odds ratio due to yearly changes) by the odds ratio due to yearly changes in the non-toner-handling group. The logarithm of this value was treated as the estimated regression coefficient for the interaction between toner-handling work and survey year in the GEE logistic regression model analysis. If the value is significantly higher than 1.0, it indicates that the odds ratio for the yearly change of each symptom in the toner exposure group is higher than that in the control group, and the exposure might be a risk factor for each symptom. Conversely, if the value is significantly lower than 1.0, it indicates that the odds ratio in the toner exposure group is lower than that in the control group. The estimated regression coefficient for toner-handling work and survey year corresponded the logarithm of the odds ratio for respiratory symptoms in the toner-handling group relative to the control group at baseline survey and the logarithm of the odds ratio for yearly changes in the control group, respectively. In all tests, the significance level was less than 0.05. SPSS23.0J analytical software (IBM) was used.

### *2.8. Ethical Considerations*

The following items were confirmed before study initiation: Voluntary participation in the study by participants, measures for protecting the privacy of participants, methods for ensuring understanding and obtaining consent from the participants, notice of study results to the participants, prohibition of the use of participant data for purposes other than the study objective, destruction of survey information following the end of the survey, potential risks and detriments to participants, and the countermeasures to take upon their occurrence. Details of these items were approved by the Ethics Committee of Medical Research, University of Occupational and Environmental Health, Japan.

## 3. Results

### *3.1. Participants*

Of the total 1504 subjects, 9 toner-handling workers, and 2 non-toner-handling workers did not complete the baseline survey. The reasons for refusal to participate were not related to whether or not they had respiratory diseases. The final number of participants by the group was 909 in the toner-handling group and 584 in the non-toner-handling group. Of the 1493 participants who completed the baseline survey, 25 lacking work history data (22 toner-handling workers and 3 non-toner-handling workers) were excluded, and the remaining 1468 subjects (887 toner-handling workers and 581 non-toner-handling workers) were selected for the analysis set.

At the time of the baseline survey, none of the participants had been affected by any of the diseases set as endpoints (Granulomatous interstitial pneumonia, pneumoconiosis, and lung cancer), apart from bronchial asthma. The prevalence of asthma was comparable between the toner-handling and non-toner-handling groups. The mean number of surveys the subjects completed was 8.8 out of a total of 10, and the mean length of follow-up (time elapsed from the baseline to the last observation) was 8.9 years. These parameters did not significantly differ between the toner-handling group and the non-toner-handling group. Cohort characteristics at study initiation are shown in Table 1. The chi-square test and Fisher exact test were performed for qualitative variables, and the simple t-test and Welch t-test were performed for quantitative variables to compare the characteristics of the toner-handling and non-toner-handling groups. As for quantitative variables, Levene's test was performed, with a simple t-test applied for equal variance and a Welch *t*-test for unequal variance. Several baseline characteristics of both groups differed in a statistically significant way. Mean body mass index (BMI) was significantly higher in the non-toner-handling group, whereas the proportion of hazardous-material handling workers, the prevalence of chronic phlegm, and the prevalence of shortness of breath were higher in the toner-handling group.

During the period from the first survey to the last survey (10th survey), 203 toner-handling workers and 167 non-toner-handling workers withdrew from the study. When these participants withdrew their consent, withdrawal documents were obtained and checked to confirm that their reasons were not related to the onset of respiratory diseases such as granulomatous interstitial pneumonia, pneumoconiosis, and lung cancer. Table 2 compares the baseline data of subjects who withdrew from the study and those who completed follow-up. While there was no significant difference in baseline data between those who withdrew and those who completed follow-up in the non-toner-handling group, subjects who withdrew were significantly older than those who completed follow-up in the toner-handling group.

**Table 1.** Participants' baseline characteristics.

| **Characteristic** | **Toner-Handling Group** | | **Non-Toner-Handling Group** | | ***p*-Value** |
|---|---|---|---|---|---|
| | ***n* = 887** | | ***n* = 581** | | |
| | **Mean (SD) no./total no. (%)** | | **Mean (SD) no./total no. (%)** | | |
| Age (years) | 38.7 | (7.1) | 38.5 | (6.5) | 0.68 |
| BMI (kg/m2) | 23.3 | (2.9) | 23.7 | (2.9) | 0.02 |
| Current smoker | 454/887 | (51.2) | 272/551 | (46.8) | 0.11 |
| Proportion (%) of participants with disease | | | | | |
| Asthma | 84/887 | (9.5) | 60/581 | (10.3) | 0.59 |
| Allergic rhinitis | 453/887 | (51.1) | 280/581 | (48.2) | 0.29 |
| Allergic dermatitis | 185/887 | (20.9) | 129/581 | (22.2) | 0.56 |
| Pneumonia | 4/887 | (0.5) | 2/581 | (0.3) | 1.00 |
| Sinusitis | 27/887 | (2.7) | 11/581 | (1.9) | 0.38 |
| Proportion (%) of hazardous-material-handling workers | | | | | |
| Dust-other than toner work | 26/887 | (2.9) | 2/581 | (0.3) | <0.001 |
| Organic-solvent-handling work | 233/887 | (26.3) | 17/581 | (2.9) | <0.001 |
| Proportion (%) of subjects with subjective respiratory symptom complaints | | | | | |
| Chronic cough | 54/880 | (6.1) | 23/575 | (4.5) | 0.20 |
| Chronic phlegm | 88/883 | (10.0) | 35/577 | (6.1) | 0.009 |
| Chronic cough and phlegm | 53/887 | (6.0) | 31/581 | (5.3) | 0.65 |
| Wheezing without asthmatic response | 2/883 | (0.2) | 3/577 | (0.5) | 0.39 |
| Shortness of breath | 113/887 | (12.7) | 33/580 | (5.7) | <0.001 |

*p*-value for the quantitative variable was obtained with the simple t-test and Welch's *t*-test. *p*-value for the qualitative variable was obtained by Fisher's exact test. BMI: Body mass index.

**Table 2.** Comparison of participants' baseline characteristics and respiratory symptoms between those who withdrew and those who completed follow-up.

| Characteristic | Toner-Handling Group | | | | | Non-Toner-Handling Group | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Completed | | Withdrew | | *p*-Value | Completed | | Withdrew | | *p*-Value |
| | *n* = 684 | | *n* = 203 | | | *n* = 414 | | *n* = 167 | | |
| | Mean (SD) no./total no. (%) | | Mean (SD) no./total no. (%) | | | Mean (SD) no./total no. (%) | | Mean (SD) no./total no. (%) | | |
| Age (years) | 38 | (6.9) | 41.2 | (7.2) | <0.001 | 38.6 | (6.1) | 38.3 | (7.4) | 0.63 |
| BMI (kg/m$^2$) | 23.3 | (2.9) | 23.5 | (3.0) | 0.43 | 23.7 | (3.0) | 23.6 | (2.9) | 0.79 |
| Current smoker | 356/684 | (52.0) | 98/203 | (48.3) | 0.38 | 184/414 | (44.4) | 88/167 | (52.7) | 0.08 |
| Proportion (%) of subjects with disease | | | | | | | | | | |
| Asthma | 68/684 | (9.9) | 16/203 | (7.9) | 0.42 | 40/414 | (9.7) | 20/167 | (12.0) | 0.45 |
| Allergic rhinitis | 650/684 | (51.2) | 13/203 | (50.7) | 0.94 | 201/414 | (48.6) | 79/167 | (47.3) | 0.85 |
| Allergic dermatitis | 148/684 | (21.6) | 37/203 | (18.2) | 0.33 | 95/414 | (22.9) | 34/167 | (20.4) | 0.58 |
| Pneumonia | 4/684 | (0.6) | 0/203 | (0.0) | 0.58 | 2/414 | (0.5) | 0/167 | (0.0) | 1.00 |
| Sinusitis | 17/684 | (2.5) | 7/203 | (3.4) | 0.46 | 6/414 | (1.4) | 5/167 | (3.0) | 0.31 |
| Proportion (%) of hazardous-material-handling workers | | | | | | | | | | |
| Dust other than toner work | 26/684 | (3.8) | 0/203 | (0.0) | 0.002 | 1/414 | (0.2) | 1/167 | (0.6) | 0.49 |
| Organic-solvent work | 175/684 | (25.6) | 58/203 | (28.6) | 0.41 | 12/414 | (2.9) | 5/167 | (3.0) | 1.00 |
| Proportion (%) of subjects with subjective respiratory symptom complaints | | | | | | | | | | |
| Chronic cough | 43/678 | (6.3) | 11/202 | (5.4) | 0.74 | 40/411 | (4.9) | 6/164 | (3.7) | 0.66 |
| Chronic phlegm | 70/682 | (10.3) | 18/201 | (9.0) | 0.69 | 25/411 | (6.1) | 10/166 | (6.0) | 1.00 |
| Chronic cough and phlegm | 45/684 | (6.6) | 8/203 | (3.9) | 0.18 | 21/414 | (5.1) | 10/167 | (6.0) | 0.69 |
| Wheezing without asthmatic response | 1/684 | (0.1) | 1/201 | (0.5) | 0.40 | 3/411 | (0.7) | 0/166 | (0.0) | 0.56 |
| Shortness of breath | 82/684 | (12.0) | 31/203 | (15.3) | 0.31 | 20/414 | (4.8) | 13/166 | (7.8) | 0.17 |

*p*-value for the quantitative variable was obtained by the simple t-test and Welch's t-test. *p*-value for the qualitative variable was obtained by Fisher's exact test. BMI: Body mass index.

### *3.2. Toner Exposure Assessment and Subject Grouping*

Respirable dust collected on the personal dust sampler filters was confirmed to be toner-derived based on electronic microscopy observations and infrared spectroscopy [13]. We found that individual exposure concentrations differed among the five work categories, being significantly higher in machine-recycling work and toner-manufacturing work than in the other work categories. The mean of baseline 8-hour time-weighted average (TWA-8h) (SD) exposure concentration by work category was as follows: A total of 0.989 (0.786) mg/m$^3$ for toner and copy machine recycling (hereafter referred as "recycling"), 0.203 (0.441) mg/m$^3$ for toner manufacturing, 0.034 (0.030) mg/m$^3$ for toner development, 0.019 (0.063) mg/m$^3$ for toner and copy machine development, and 0.020 (0.060) mg/m$^3$ for customer service. Based on these exposure concentration differences at the baseline survey, we divided the toner-handling group into two subgroups, as follows: Those engaged in recycling and toner manufacturing (high-concentration toner exposure group) and the others (low-concentration toner exposure group). Of the 887 subjects in the toner-handling group, 49 were engaged in recycling work and toner manufacturing work (high-concentration toner exposure group) and 838 were engaged in other work (low-concentration toner exposure group). The non-toner-handling group served as the control group. We assessed data across the three groups. It should be noted, however, that even in the high-concentration toner exposure group, the TWA-8h value was much lower than the 3.0 mg/m$^3$ maximum allowable level for unspecified particles, defined as the threshold limit value-the time-weighted average (TLV-TWA), recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) [24]. Since work environment and procedural improvements, such as sufficient control of general and regional ventilation, were implemented to reduce worker exposure after the baseline survey, differences in exposure concentration among work categories decreased over the survey years.

### *3.3. Incidence of Respiratory Diseases*

No new onset of granulomatous interstitial pneumonia and pneumoconiosis was observed during the 10-year period. In contrast, four subjects developed lung cancer during the follow-up period; among whom, three were toner-handling workers (all engaged in low-concentration exposure work, including 1 smoker) and there was one non-toner-handling workers (smoker).

The incidence rate of lung cancer per 100,000 person-years was 38.4 (95% confidence interval (CI):13.0–112.8) in the toner-handling group and 19.5 (95% CI: 3.4–110.4) in the non-toner-handling group. The ratio for the incidence rate of lung cancer in the toner handling group relative to the non-toner-handling group was 1.97 (95% CI: 0.20–18.9), indicating no significant difference.

The prevalence of asthma in each year of the observation period varied from 0.7% to 2.1%, but was similar between the toner-handling group and the non-toner-handling group in all years. Using GEE analysis with the prevalence of asthma as the independent variable and toner-handling work, survey year, and interaction between toner-handling work and survey year as dependent variables, the quotient of the odds ratio for yearly changes in the toner handling group divided by the odds ratio in the non-toner-handling group was estimated to be 1.04 (95% CI: 0.93–1.17; $P = 0.49$).

### *3.4. Subjective Respiratory Symptoms*

#### 3.4.1. Panel Data Analysis

The prevalence of subjective respiratory symptoms in the toner-handling group and the non-toner-handling group is shown in Table 3. The prevalence of wheezing without asthmatic response and chronic phlegm were similar between the two groups in all years. Significant differences in the prevalence of chronic cough and chronic cough and phlegm were sporadically observed throughout the observation period. Meanwhile, the prevalence of shortness of breath was significantly higher in the toner-handling group in a number of years.

### 3.4.2. Longitudinal Analysis

Table 4 shows the estimated effect of toner exposure on yearly changes of each subjective respiratory symptom (the quotient of the odds ratio for yearly changes in the toner-handling group divided by the odds ratio in the non-toner-handling group) determined using Models 1 to 3. There was no significant effect of toner exposure on any of the five symptoms, irrespective of the presence or absence of adjustment for confounding factors. Model 3 showed the highest fit for four of the five symptoms, as follows: Chronic cough, chronic phlegm, chronic cough and phlegm, and shortness of breath. Model 2 showed the highest fit for only wheezing without asthmatic response.

There were significant differences in odds ratios at baseline in chronic phlegm, chronic cough and phlegm, and shortness of breath. The odds ratios for 3 symptoms using Model 3 were as follows: a total of 1.54 (95% CI: 1.04–2.29) for chronic phlegm, 1.63 (95% CI: 1.09–2.43) for chronic cough and phlegm, and 2.04 (95% CI: 1.43–2.92) for shortness of breath.

Table 5 shows the estimated effects obtained using Model 4 for the high-concentration toner exposure group and low-concentration toner exposure group, and the odds ratio for yearly changes in the non-toner-handling group. The odds ratio for yearly changes in the non-toner-handling group was significantly lower than 1.0 for two symptoms, as follows: Chronic cough and phlegm and shortness of breath. Toner exposure was significantly associated with wheezing without asthmatic response only in the high-concentration toner exposure group. That is, the odds ratio in the high-concentration toner exposure group was significantly lower than that of the non-toner-handling group. GEE analysis, separately at each level of toner exposure, showed that the odds ratios for yearly changes in wheezing without asthmatic response were as follows: 0.70 (95% CI: 0.53–0.93) in the high-concentration toner exposure group, 1.0 (95% CI: 0.93–1.10) in the low-concentration toner exposure group, and 0.96 (95% CI: 0.87–1.05) in the non-toner-handling group.

**Table 3.** Comparison of respiratory symptoms between the toner-handling group and non-toner-handling group.

| Symptom | Toner-Handling Group no./total no. (%) | Non-Toner-Handling Group no./total no. (%) | *p*-Value | Toner-Handling Group no./total no. (%) | Non-Toner-Handling Group no./total no. (%) | *p*-Value |
|---|---|---|---|---|---|---|
| | 1st survey | | | 2nd survey | | |
| Chronic cough | 42/835 (5.0) | 24/552 (4.3) | 0.61 | 49/827 (5.9) | 20/547 (3.7) | 0.08 |
| Chronic phlegm | 62/840 (7.4) | 30/553 (5.4) | 0.19 | 63/829 (7.6) | 27/547 (4.9) | 0.06 |
| Chronic cough and phlegm | 51/849 (6.0) | 15/558 (2.7) | 0.004 | 33/831 (4.0) | 15/553 (2.7) | 0.22 |
| Wheezing without asthmatic response | 7/849 (0.8) | 2/558 (0.4) | 0.50 | 4/829 (0.5) | 1/553 (0.2) | 0.65 |
| Shortness of breath | 86/850 (10.1) | 31/556 (5.6) | 0.003 | 74/832 (8.9) | 24/553 (4.3) | 0.001 |
| | 3rd survey | | | 4th survey | | |
| Chronic cough | 37/811 (4.6) | 25/528 (4.7) | 0.90 | 41/794 (5.2) | 19/553 (3.6) | 0.18 |
| Chronic phlegm | 55/804 (6.8) | 25/531 (4.7) | 0.13 | 57/793 (7.2) | 30/553 (5.6) | 0.31 |
| Chronic cough and phlegm | 34/824 (4.1) | 15/544 (2.8) | 0.23 | 29/802 (3.6) | 13/540 (2.4) | 0.26 |
| Wheezing without asthmatic response | 9/823 (1.1) | 4/541 (0.7) | 0.58 | 5/802 (0.6) | 4/538 (0.7) | 1.00 |
| Shortness of breath | 71/822 (8.6) | 25/544 (4.6) | 0.01 | 59/802 (7.4) | 26/540 (4.8) | 0.07 |
| | 5th survey | | | 6th survey | | |
| Chronic cough | 40/782 (5.1) | 19/532 (3.6) | 0.22 | 31/763 (4.1) | 19/509 (3.7) | 0.88 |
| Chronic phlegm | 60/787 (7.6) | 32/533 (6.0) | 0.27 | 38/763 (5.0) | 26/511 (5.1) | 1.00 |
| Chronic cough and phlegm | 34/790 (4.3) | 10/534 (1.9) | 0.02 | 26/769 (3.4) | 12/521 (2.3) | 0.32 |
| Wheezing without asthmatic response | 8/790 (1.0) | 5/534 (0.9) | 1.00 | 5/766 (0.6) | 4/517 (0.8) | 1.00 |
| Shortness of breath | 57/791 (7.2) | 15/534 (2.8) | <0.001 | 57/771 (7.4) | 11/521 (2.1) | <0.001 |
| | 7th survey | | | 8th survey | | |
| Chronic cough | 39/738 (5.3) | 15/502 (3.0) | 0.07 | 28/735 (3.8) | 20/502 (4.0) | 0.88 |
| Chronic phlegm | 40/740 (5.4) | 23/502 (4.6) | 0.60 | 39/738 (5.3) | 30/503 (6.0) | 0.62 |
| Chronic cough and phlegm | 26/753 (3.5) | 12/506 (2.4) | 0.32 | 22/747 (2.9) | 15/509 (2.9) | 1.00 |
| Wheezing without asthmatic response | 5/755 (0.7) | 4/505 (0.8) | 0.75 | 1/744 (0.1) | 4/509 (0.8) | 0.17 |
| Breathlessness | 49/756 (6.5) | 23/506 (4.5) | 0.17 | 40/748 (5.3) | 20/510 (3.9) | 0.28 |
| | 9th survey | | | 10th survey | | |
| Chronic cough | 24/717 (3.3) | 9/464 (1.9) | 0.21 | 29/669 (4.3) | 8/405 (2.0) | 0.04 |
| Chronic phlegm | 40/714 (5.6) | 17/464 (3.7) | 0.16 | 36/662 (5.4) | 19/406 (4.7) | 0.67 |
| Chronic cough and phlegm | 24/731 (3.3) | 12/479 (2.5) | 0.49 | 19/683 (2.8) | 11/413 (2.7) | 1.00 |
| Wheezing without asthmatic response | 5/730 (0.7) | 2/474 (0.4) | 0.71 | 3/677 (0.4) | 1/413 (0.2) | 1.00 |
| Shortness of breath | 50/730 (6.8) | 17/480 (3.5) | 0.01 | 47/681 (6.9) | 9/412 (2.2) | 0.001 |

**Table 4.** Effects of toner-handling work on respiratory symptoms by model.

| | Model 1 | | | | Model 2 | | | | Model 3 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Estimate** | **95% CI** | ***p*-Value** | **QICC** | **Estimate** | **95% CI** | ***p*-Value** | **QICC** | **Estimate** | **95% CI** | ***p*-Value** | **QICC** |
| Chronic cough | 1.02 | 0.96–1.08 | 0.53 | 5063.4 | 1.02 | 0.95–1.10 | 0.52 | 4635.9 | 1.02 | 0.95–1.09 | 0.64 | 4507.7 |
| Chronic phlegm | 0.96 | 0.91–1.01 | 0.10 | 6528.5 | 0.95 | 0.9–1.01 | 0.10 | 5760.3 | 0.95 | 0.90–1.01 | 0.09 | 5575.0 |
| Chronic cough and phlegm | 0.98 | 0.91–1.04 | 0.49 | 4391.1 | 1.00 | 0.93–1.07 | 0.98 | 3963.4 | 1.00 | 0.93–1.07 | 0.99 | 3840.8 |
| Wheezing without asthmatic response | 0.96 | 0.87–1.07 | 0.48 | 1080.0 | 1.03 | 0.91–1.16 | 0.64 | 892.8 | 1.04 | 0.92–1.17 | 0.57 | 893.5 |
| Shortness of breath | 1.00 | 0.94–1.05 | 0.90 | 6798.5 | 0.99 | 0.93–1.04 | 0.60 | 5985.0 | 0.98 | 0.93–1.03 | 0.47 | 5822.0 |

Each estimate was obtained by dividing the odds ratio for yearly changes in the toner-handling group or by the odds ratio for yearly changes in the non-toner-handling group. In all models, each subjective symptom served as an objective variable, toner handling work served as an explanatory variable, and survey year served as a covariate. In Model 1, there were no adjustments for confounding factors. In Model 2, data were adjusted for baseline age and baseline body mass index (BMI). In Model 3, data were further adjusted for smoking, asthma, allergic rhinitis, allergic dermatitis, pneumonia, sinusitis, non-toner dust-generating work, and organic solvent work. QICC: Corrected quasi-likelihood under independence model criterion (QICC)

**Table 5.** Effects of toner exposure concentration on respiratory symptoms and odds ratio for respiratory symptoms in the control group.

| | High Concentration Toner Exposure | | | Low Concentration Toner Exposure | | | Control | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Estimate** | **95% CI** | ***p*-Value** | **Estimate** | **95% CI** | ***p*-Value** | **OR** | **95% CI** | ***p*-Value** |
| Chronic cough | 0.97 | 0.79–1.21 | 0.82 | 1.02 | 0.95–1.09 | 0.61 | 0.96 | 0.9–1.02 | 0.16 |
| Chronic phlegm | 0.95 | 0.86–1.05 | 0.30 | 0.95 | 0.90–1.01 | 0.10 | 1.00 | 0.96–1.05 | 0.89 |
| Chronic cough and phlegm | 0.94 | 0.75–1.18 | 0.59 | 1.00 | 0.93–1.08 | 0.95 | 0.94 | 0.88–1.00 | 0.05 |
| Wheezing without an asthmatic response | 0.72 | 0.54–0.96 | 0.03 | 1.04 | 0.92–1.18 | 0.51 | 0.97 | 0.88–1.06 | 0.45 |
| Shortness of breath | 0.90 | 0.81–1.00 | 0.05 | 0.99 | 0.93–1.04 | 0.62 | 0.95 | 0.91–1.00 | 0.03 |

Each estimate was obtained by dividing the odds ratio for yearly changes in the high-concentration toner exposure group or low-concentration toner exposure group by the odds ratio for yearly changes in the control group.

## 4. Discussion

This 10-year cohort study of employees of a toner and copy machine manufacturing enterprise in Japan used questionnaire data to explore the chronic effects of toner-handling work on the incidence of respiratory diseases and yearly changes in subjective respiratory symptoms. We found that there was no significant difference in the incidence of respiratory diseases between the toner-handling group and the non-toner-handling group. Similarly, toner-handling work had no definitive effect on the prevalence of chronic cough, chronic phlegm, chronic cough and phlegm, or shortness of breath. However, toner-handling work had significant effects only on yearly changes in wheezing without asthmatic response in the high-concentration toner exposure group.

A number of cross-sectional studies have assessed the relationship of subjective respiratory symptoms and printing work at copy centers. All of these studies have reported a tendency for the prevalence of subjective symptoms to be higher in copy center workers than in controls [29,30]. However, high prevalence symptoms in exposed groups were not consistent in each study, including cough and wheezing, nasal obstruction, respiratory disorders, and phlegm. Additionally, a limitation of such cross-sectional studies is that they cannot irrevocably conclude that engagement in printing work at copy centers is the true cause of the respiratory symptoms, and it is impossible to rule out the effect of individual differences or non-exposure factors. Possible ways by which workers at copy centers may be exposed to toner dust include insufficient toner fusion to the paper due to a printing failure or other reasons, and toner dust leakage for any reason during replacement of toner-filled cartridges. However, such exposure is infrequent and limited. Further, these field surveys have mainly been designed to determine the health effects of fine particles emitted from printers during the printing process at copy centers. It is difficult to consider whether the effects are due to exposure to printer emission or toner dust in these studies.

Several cohort studies at toner manufacturing factories were conducted for similar purposes to our study [12–15]. All of these studies consistently reported a tendency for the prevalence of respiratory symptoms, such as cough, phlegm, wheezing, and shortness of breath, to be higher in the toner exposure group, although no significant differences have been found between the toner-handling group and non-toner-handling group. A cohort study that monitored changes in the number of new onsets of symptoms showed that the incidence of chronic cough was significantly higher in the exposure group. It is important to note, however, that in all of these cohort studies, respiratory symptoms were inconsistent with the severity of objective findings, such as those on chest X-ray photograms and respiratory function tests. The authors of these cohort studies suggested that the trend in the high prevalence of respiratory symptoms that are not consistent with objective findings were related to the potential effects of individual differences in response to dust exposure or allergic diseases.

In this study, because the probability of symptom complaints due to toner exposure was considered to be correlated within the same subject, we applied the GEE for analysis of longitudinal data. In addition, because longitudinal data is dependent on baseline values, it is necessary to distinguish whether significant differences in responses between the two groups are due to baseline intergroup differences or the subsequent exposure. The latter is important for assessing the effect of toner exposure. For this reason, we examined the estimated regression coefficients for the interaction between toner-handling work and survey year as an index of the effect of toner-handling work.

Using GEE analysis, the adjusted likelihood of symptom complaints at baseline for chronic phlegm, chronic cough and phlegm, and shortness of breath was significantly higher in the toner-handling group. Although there was no significant difference in chronic cough, the prevalence in the toner-handling group tended to be higher at baseline as compared to the non-toner-handling group.

For chronic cough and chronic phlegm, neither the effect of toner exposure nor yearly changes in the control group were significant (Table 5). This suggested that the tendency for the prevalence to be higher in the toner-handling group than in the non-toner-handling group during the follow-up period (Table 3) was probably attributable to the degree of difference between the two groups observed at baseline remaining unchanged over time.

Toner exposure also had no effect on chronic cough and phlegm and shortness of breath, while the odds ratio for yearly change of both symptoms was significantly lower than 1.0. For this reason, as shown in Table 3, we assumed that the prevalence of both symptoms decreased with a similar slope over the follow-up period, but the difference between the two groups remained unchanged.

Due to the same limitations as the cross-sectional studies, it is difficult to identify the true cause of the difference between the two groups observed at baseline. However, the difference may be due to information bias. We supposed that the symptoms of phlegm, cough and phlegm, and shortness of breath, could be well recognized as common symptoms when in poor general condition, such as a common cold. That is, the number of participants with an awareness of their symptoms may have increased after they developed an understanding of the study's objective [31].

For wheezing without asthmatic response, comparison of the toner-handling group and the non-toner-handling group showed no effect of toner exposure, baseline difference, and yearly changes. However, analysis of the three exposure levels showed that only the high-concentration toner exposure had a significantly lower odds ratio than the control. The number of subjects who complained of wheezing without asthmatic response in the high-concentration toner exposure group was 1 in the second year, 1 in the third year, and 0 in other years. As the sample size of the high-concentration toner exposure group was very small ($n = 49$), the prevalence appeared large (2.0%), even though only 1 subject complained of the symptom. As shown in Table 3, the prevalence of wheezing without asthmatic response in all toner-handling workers was 0.1% to 1.1%. Therefore, the observed improvement in the prevalence of wheezing without asthmatic response in high-concentration toner exposure group may have resulted from an overestimation due to the small sample size. In other words, it is unlikely that the odds ratio decreased due to high-concentration exposure. In all cases, toner dust exposure did not increase the prevalence of wheezing without asthmatic response.

Smoking rates among all subjects in this study were 50.9% at the 2003 baseline survey, decreasing to 32.2% at the final 2013 survey. There was no significant difference in the current smoking rate at the final survey between the two groups; at 34.3% in the toner-handling group and 29.1% in the non-toner-handling group. The smoking rate of Japanese men in their 30s in 2003 was 56.8%, decreasing to 39.5% in 2013 [32,33]. In other words, the smoking rate in this cohort was lower than that of the general population of Japanese men. Smoking may have combined effects on simultaneous exposure with other harmful substances. We also considered the possibility of combined effects of toner and smoking on five chronic respiratory symptoms. In the GEE analysis using Model 3, only two symptoms, chronic phlegm and shortness of breath, had a significant interaction effect among toner, smoking, and year. Using the GEE analysis again for these two symptoms, we obtained the odds ratios for the yearly change in both the toner-handling smoking group and the non-toner-handling non-smoking group. For both symptoms, there was no significant yearly change in the non-toner-handling non-smoking group. In contrast, the odds ratio for yearly change was significantly lower than 1 in the toner-handling smoking group. This could be due to the effect of the decrease in the smoking rate during the observation period in the toner-handling smoking group. In the non-toner-handling non-smoking group, the smoking rate, of course, did not change, while the smoking rate in the toner-handling smoking group decreased from 100% to 63.2% at the final survey. At the least, no combined effect of simultaneous toner and smoking exposure on respiratory symptoms was observed.

Formaldehyde (FA) is frequently used as a component of building materials, adhesive agents, preservative agents, and so on, and is also contained in combustion exhaust gas generated from cigarette smoke and heating appliances. As a consequence of its various uses, FA is widely present as a pollutant affecting air quality in the workplace. FA is known to have irritation effects on the human respiratory system, and the carcinogenicity of FA and the effects on exacerbation of allergic diseases also have been investigated [34]. Therefore, when we examined the health effects of toner, it was necessary to consider the effects of FA, an indoor air pollutant that participants may be exposed to, as a factor affecting the respiratory system other than toner. In 1997, the Ministry of Health, Labor and Welfare defined a guideline for indoor concentration of chemical substances in Japan [35], and the standard for FA was set to 0.08 ppm. In response to this guideline, the Japanese Ordinance on Health Standards in the office was amended in 2004 [36]. In compliance with this regulation, the concentration of FA in the air supplied to the workplace where workers are constantly engaged is required to be 0.08 ppm or less. Several previous studies reported that the threshold for FA-induced irritation effects was about between 0.4 ppm and 1 ppm [37–40]. In this study, we analyzed respirable dust exposed to toner-handling workers by personal exposure measurements, but did not perform the environmental measurement of FA in the workplace. However, during almost all survey periods, the indoor air environment management at the survey site complied with this regulation, and appropriate ventilation was provided, so we thought that FA concentration was well below the estimated threshold for irritation effects. In addition, it has been suggested that people with allergic diseases may become more symptomatic when exposed to gaseous FA [41]. We responded to this suggestion by adjusting the effect of allergic diseases with statistical analysis. Consequently, we thought that the effects of FA exposure on the respiratory system of the participants were well controlled.

In our analysis taking into consideration the difference in baseline between the toner-handling group and the non-toner-handling group, no effects of toner-handling work were observed on any symptom or disease occurrence. This suggested that one of the possible reasons the trend in the high prevalence of the subjective symptoms was inconsistent with the objective findings reported in other previous epidemiological studies was the influence of differences between the toner-handling group and the non-toner-handling group at baseline. In terms of the low respiratory toxicity of toner exposure, the results obtained by this cohort study on subjective respiratory symptoms and respiratory diseases showed the same direction as the results of long-term inhalation exposure studies in animals [42–44], and objective findings in the previous cohort studies [12–15].

This study had a number of limitations. First, the number of samples in the high-concentration toner exposure group was 49, which may have been insufficient to detect the difference among three independent group proportions. In accordance with a common industrial health survey guide, Japanese toner manufacturers are currently cooperating to implement cohort surveys to determine the health effects of toner dust at individual companies [45]. In the future, pooled analyses based on such survey results from multiple companies will be useful for analyzing the dose-response relationship between toner dust exposure and symptoms. Second, a 10-year survey period may have been insufficient. Onsets of the endpoint respiratory disease, for the most part, require long exposure times. It may be necessary to continue to follow-up the participants in the toner-handling group. Third, because follow-up was discontinued with the occurrence of the endpoint disease, we may have missed other endpoint diseases that occurred after the follow-up. Accordingly, it is possible that the health risk of toner-handling work was estimated to be low. Fourth, because toner-handling work tends to be associated with larger physical workloads than non-toner-handling work, employees with critical health issues may have been engaged in toner-handling work. This healthy worker bias [30] may have led to an underestimation of the risk associated with toner-handling work. Finally, the toner exposure concentrations at the study sites may have been low. This may be because the work environment was appropriately managed to prevent dust scattering (using exhaust equipment). Moreover, workers who frequently worked with toner were instructed to observe the rules for respiratory mask expiration and periodic exchanging of filters. In addition, from the perspective of safety and hygiene, toner dust concentrations were measured outside the respiratory masks. The actual levels inhaled were therefore likely lower than the measured toner dust concentrations.

## 5. Conclusions

We explored the effect of toner-handling work on the incidence of granulomatous interstitial pneumonia, pneumoconiosis, and lung cancer; changes in the prevalence of asthma; and changes in the prevalence of subjective respiratory symptoms in an occupational cohort in a Japanese toner and copy machine manufacturing enterprise. A GEE analysis that adjusted for confounding factors and accounted for the correlation of within-subject data showed that toner-handling work was not associated with exacerbation of these outcomes. This study suggests that toner-handling work had little adverse effect on human health in work environments with sufficiently controlled ventilation.

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