

# Frequency of Persistent Cough and Trends in Seeking Medical Care and Treatment—Results of an Internet Survey

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## ABSTRACT

**Background:** Cough is a frequently encountered symptom and can be indicative of a serious underlying disease. However, no studies have investigated the incidence of cough in the general population in Japan, the diseases causing cough or the treatments administered.

**Methods:** We sent a screening survey to 29,085 randomly selected individuals and a more detailed survey to the first 1,000 individuals with cough who agreed to participate and provided consent. The survey included questions to determine the duration of cough, disturbances of daily living and whether the individual had consulted a physician.

**Results:** The prevalence of cough among the general population was 10.2%. There was no difference in cough frequency between males and females or across age groups. The prevalence of prolonged or chronic cough (cough lasting  $\geq 3$  weeks) was 35.8% and the duration of cough increased with age. Women were more troubled by cough than men were. “Feeling ashamed to cough in front of other people” (49.0%) and “causing trouble to other people” (42.8%) were the main reasons for feeling troubled by cough. More than 60% of surveyed individuals were not receiving care and 44.0% had no plans to visit a medical facility. Although cold was the most common cause of cough overall, asthma was the main cause among individuals with cough lasting  $\geq 8$  weeks.

**Conclusions:** In this large-scale cohort study, many respondents were unwilling to visit their doctor, despite having chronic cough. Improvements in educational campaigns are needed to encourage people with chronic cough to visit a doctor.

## KEY WORDS

activities of daily living, cough, epidemiology, etiology, health care seeking behavior

## INTRODUCTION

Cough is the most frequently encountered symptom of respiratory diseases in clinical practice and is an important symptom that can reflect a significant disease. Persistent cough can arise from diseases such as lung cancer and pulmonary tuberculosis, which should not be overlooked. Even in the absence of such diseases, cough often interferes with daily living and sleep. It can also reflect other treatable diseases

such as cough-variant asthma and atopic cough. Therefore, accurate differential diagnosis of the underlying disease is critical in patients presenting with persistent cough. Persistent cough consists of prolonged cough (lasting 3-8 weeks) and chronic cough (lasting  $\geq 8$  weeks). Chronic cough has been defined as “cough lasting longer than 8 weeks as the only symptom and whose cause is not apparent by physical examination and routine testing such as CXR and spirometry”.<sup>1</sup>

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Conflict of interest: The online survey was carried out by Abbott Japan.

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Received 4 September 2011. Accepted for publication 2 April 2012.

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To date, no cohort study has been conducted in Japan to investigate the incidence of cough in the general population. Furthermore, no studies have surveyed the causes of cough or the treatments administered. Most epidemiological studies of the frequency of cough encountered in clinical practice were conducted in Western countries.<sup>2-13</sup> In these studies, the incidence of cough in the general population was 9-33%, and the frequency of chronic cough was substantially higher in smokers than in non-smokers.<sup>2-13</sup>

To collect information about the diagnosis and treatment of persistent cough in Japan, we conducted an Internet survey of the presence of cough, its influence of daily living, visits to medical facilities and treatment in the general population of Japan.

## METHODS

### SURVEY METHODS

The survey was conducted on-line using a panel of individuals voluntarily registered with a research company (Nielsen; Tokyo, Japan) via the Internet. From 998,418 registered individuals aged  $\geq 16$  years uniformly reflecting the demographic make-up of the census, 29,085 individuals were randomly selected for this survey. An e-mail requesting participation in the survey was sent to these individuals, and responses about the presence/absence of cough were collected from 10,505 individuals (screening survey). The first 1,000 individuals with cough symptoms were enrolled in the main survey regardless of their locations. The cut-off of 29,085 individuals in the initial screen was selected because it was the number of initial queries at which we obtained responses from 1,000 individuals who reported the presence of cough and consented to participation.

### QUESTIONNAIRE METHOD

In the screening survey, the participants were asked to comment on the presence/absence of 12 symptoms experienced on the day of the survey, including cough, nasal discharge and itchiness of the eyes (Table 1). The second questionnaire, sent to the first 1,000 individuals who reported the presence of cough, recorded the duration of cough, disturbances of daily living and whether the individual had consulted a physician, for example (abridged version shown in Table 1; the full survey is available as Supplementary Table 1 at the online journal site). Consent to use the questionnaire results was obtained from the subjects at the time of survey.

### SURVEY PERIOD

The survey was conducted from January 19 to 24, 2011. Although the incidence of upper respiratory tract infections is likely to be higher during this period, individuals with cough due to infections would be classified as having acute cough on the basis of the question regarding duration of cough. January

was selected because the influence of pollinosis was likely to be minimal at that time.

## RESULTS

### SUBJECTS

The mean age of the 1,000 individuals who participated in the survey was 55.3 years, 49.7% were aged  $\geq 60$  years, and 61.8% were males. Of 971 individuals aged  $\geq 20$  years, 22.2% were smokers at the time of the survey, 36.1% were ex-smokers and 41.6% were non-smokers. Among smokers, the mean number of cigarettes smoked was 17.9 per day, and the mean duration of smoking was 31.6 years. Among ex-smokers, the mean duration of smoking was 21.5 years. The prevalence of food allergy was 11.0%. A history of asthmatic symptoms was reported by 17.5% of the individuals surveyed, and 14.2% had a history of symptoms of atopic dermatitis.

### FREQUENCY OF COUGH AND PRESENCE OF SYMPTOMS OTHER THAN COUGH

Among the 10,505 individuals who responded to the screening survey, 1,073 (10.2%) complained of cough (Fig. 1). The prevalence of cough by age was 7.5% in participants aged 10-19 years, 9.4% in participants aged 20-29 years, 10.7% in participants aged 30-39 years, 10.2% in participants aged 40-49 years, 10.1% in participants aged 50-59 years, 9.9% in participants aged 60-69 years, and 10.9% in participants aged  $\geq 70$  years. There was no marked bias towards any age group in terms of the prevalence of cough. There was also little difference in the prevalence of cough between males and females in any age group (Table 2).

Symptoms other than cough that were reported by the 1,000 individuals complaining of cough included nasal discharge/congestion (59.3%), throat discomfort (56.0%), sputum (44.2%), sneeze (36.8%), ocular pruritus/congestion (34.6%), malaise (22.5%), headache (21.9%), wheeze (7.2%), fever (6.4%), and others (4.6%).

### DURATION AND FREQUENCY OF COUGH

The mean duration of cough among the 1,000 individuals surveyed was 3.8 weeks. Among participants with cough symptoms, the prevalence of prolonged or chronic cough (cough lasting  $\geq 3$  weeks) was 35.8% (40.1% of the men surveyed and 28.8% of the women surveyed) and the prevalence of chronic cough (cough lasting  $\geq 8$  weeks) was 23.2% (27.7% of the men surveyed and 16.0% of the women surveyed) (Table 2, Fig. 2). When analyzed by age, the duration of cough increased with age, with the percentages of individuals complaining of cough lasting  $\geq 8$  weeks being higher among participants aged 60-69 years (29.3%) and  $\geq 70$  years (27.9%) than among those aged  $< 60$  years (17.9%).

The mean daily frequency of cough was 6.6. A daily frequency of 5-9 coughs was reported by 24.9% of the

**Table 1** Abridged questionnaire**■ Screening survey**

At present, do you have any of these symptoms? (Multiple choices allowed from the following 12 items: "nasal discharge/congestion"; "ocular pruritus/congestion"; "sneeze"; "throat discomfort"; "malaise"; "headache"; "cough"; "fever"; "sputum"; "wheeze"; "others"; and "no symptom")

**■ Main survey**

- Q1 You replied that at present, "cough symptoms are present." for how long have the symptoms lasted? (<1 week/1-3 weeks/3-8 weeks/8 weeks or longer)
- Q2 How many times does continuous coughing occur in 1 day? (open-ended response)
- Q3 On how many days does continuous coughing occur in 1 week? (open-ended response)
- Q4 How troublesome are your cough symptoms at present? ("problems in daily living", "no problems in daily living, but troublesome", "no problem in daily living and causing almost no concern", "causing no concern at all")
- Q5 How troublesome are the cough symptoms in your daily living? (Multiple choices allowed from the following 15 items: "waking during sleep at night/waking early before dawn"; "unable to fall asleep"; "unable to concentrate on work, housework or learning"; "having difficulty during eating"; "having difficulty when driving a car"; "having difficulty in conversation"; "restricted as to what can be done or eaten"; "causing trouble to other people"; "feeling ashamed to cough before other people"; "having difficulty while on the train"; "having difficulty when going outdoors"; "restriction on activity, unable to exercise"; "having urinary incontinence"; "others" [two spaces available for other specific problems]; and "no particular problem")
- Q6 Which items are especially troublesome? (Select the most troublesome items)
- Q7 Have you consulted a physician at a clinic or hospital, for your current cough symptoms? ("currently under the care of a physician", "consulted before but not at present", "not yet consulted but intend to", "not yet consulted, and do not intend to do so in the future")
- Q8 Do you want to know the underlying disease that is causing the current cough symptoms?
- Q9 Subjects who replied "consulted before but not at present" or "not yet consulted, and do not intend to do so in the future" in Q7, what is the reason that you have not consulted a physician? (Select from the following 13 items + open ended response: "feels not so severe enough to receive care"; "too busy to take the time to visit"; "bother"; "high medical expenditure"; "I hate drugs"; "insufficient efficacy of the drugs prescribed"; "afraid of official diagnosis"; "because of temporary symptom, it may remit with the course of time"; "do not trust doctors/hospitals"; "cough is not a disease"; "I don't know where to visit"; "no appropriate hospital in the neighborhood"; "enough with nonprescription drug"; and "others")
- Q10 Do you take any of the following drugs in relation to your current cough symptoms? ("over-the-counter drugs", "Chinese herbal medicine", "supplements", "other drugs", "do not take drugs")
- Q11 To what degree are you satisfied with the effects? ("satisfied", "fairly satisfied", "not very satisfied", "not satisfied")
- Q12 Subjects who replied "currently under the care of a physician" or "consulted before but not at present" in Q7, what led you to consult a physician? (Select from the following 13 items + open-ended response: "symptoms became worse"; "indicated at health examination"; "indicated at comprehensive medical examination"; "nonprescription drug was not effective"; "based on TV commercial"; "based on feature program on TV"; "based on the advertisement on newspaper or magazine"; "based on feature article on newspaper or magazine"; "based on radio program"; "based on the information on the Internet"; "recommended by doctor or healthcare professional"; "recommended by family member"; "recommended by friends/acquaintance"; and "others")
- Q13 What diagnosis have you received for the cough symptoms? (Select from the following 14 items + open-ended response: "cold"; "pneumonia"; "asthma"; "cough variant asthma"; "chronic bronchitis"; "pertussis"; "atopic cough"; "sinusitis"; "pulmonary emphysema"; "chronic obstructive pulmonary disease"; "gastroesophageal reflux disease"; "lung cancer"; "tuberculosis"; "others"; and "unknown")
- Q14 Subjects who replied "currently under the care of a physician" in Q7, how long were you under the care of a physician at a hospital or clinic? ("<1 month", "1 week-1 month", "1-3 months", "≥3 months")

Note: The full questionnaire sent to the participants, is available as Supplementary Table 1 at the online journal site.

subjects, and a frequency of  $\geq 10$  was reported by 24.8% of the subjects. Thus, about half of all individuals with cough had a daily cough frequency  $\geq 5$ . The frequency of cough could not be determined in 12.3% of the participants. On average, cough occurred on 5.5 days of the week, with 51.2% of the participants reporting that they coughed every day (Fig. 3). The time of the day at which cough occurred was before waking in 16.9% of subjects, at the time of getting up in the morning in 30.7%, in the morning (from waking until noon) in 27.0%, in the afternoon in 35.7%, in the evening in 31.1%, at night (until bedtime) in 28.4%, at

bedtime in 23.6%, during sleep in 15.9%, and throughout the day in 27.2%. Thus, the occurrence of cough was not influenced by the time of day.

### INFLUENCE OF COUGH ON DAILY LIVING

When asked about the influence of cough on daily living, 23.4% of those surveyed reported having "no problem in daily living and almost no concern with cough", 4.0% reported having "no concern", and 65.6% reported having "no problem in daily living, but finding the cough troublesome" (Fig. 4). By sex, 79.3% of women found cough "troublesome" or "causing prob-

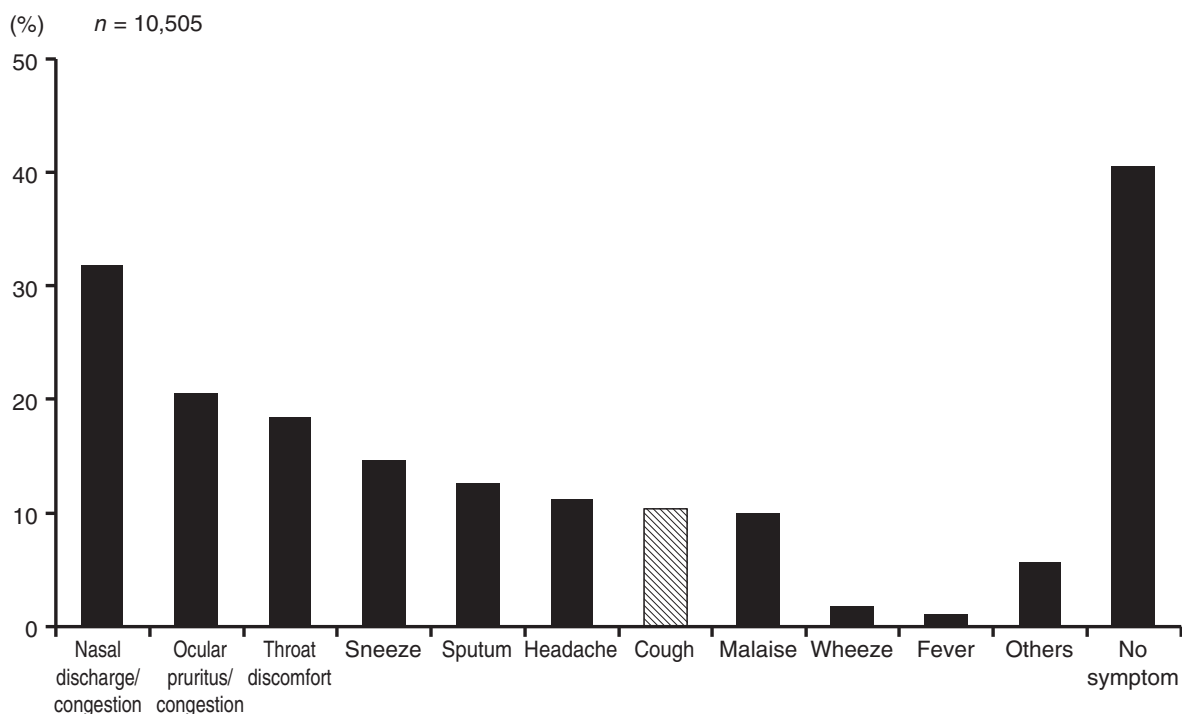


**Fig. 1** Frequency of clinical symptoms in the surveyed population.

**Table 2** Prevalence of cough by age, sex and duration

|           | No. of screening respondents | No. with cough symptoms | Prevalence of cough | No. of respondents included in the main survey | ≥3 weeks (prolonged/chronic cough) |       | ≥8 weeks (chronic cough) |       |
|-----------|------------------------------|-------------------------|---------------------|------------------------------------------------|------------------------------------|-------|--------------------------|-------|
|           |                              |                         |                     |                                                | Persons                            | %     | Persons                  | %     |
| Total     | 10,505                       | 1,073                   | 10.2%               | 1,000                                          | 358                                | 35.8% | 232                      | 23.2% |
| All men   | 6,460                        | 670                     | 10.4%               | 618                                            | 248                                | 40.1% | 171                      | 27.7% |
| 10-19 yrs | 140                          | 6                       | 4.3%                | 6                                              | 2                                  | 33.3% | 2                        | 33.3% |
| 20-29 yrs | 202                          | 19                      | 9.4%                | 19                                             | 3                                  | 15.8% | 3                        | 15.8% |
| 30-39 yrs | 453                          | 43                      | 9.5%                | 35                                             | 12                                 | 34.3% | 9                        | 25.7% |
| 40-49 yrs | 800                          | 87                      | 10.9%               | 74                                             | 26                                 | 35.1% | 15                       | 20.3% |
| 50-59 yrs | 1,223                        | 129                     | 10.5%               | 120                                            | 45                                 | 37.5% | 32                       | 26.7% |
| 60-69 yrs | 1,710                        | 168                     | 9.8%                | 155                                            | 71                                 | 45.8% | 51                       | 32.9% |
| ≥70 yrs   | 1,932                        | 218                     | 11.3%               | 209                                            | 89                                 | 42.6% | 59                       | 28.2% |
| All women | 4,045                        | 403                     | 10.0%               | 382                                            | 110                                | 28.8% | 61                       | 16.0% |
| 10-19 yrs | 260                          | 24                      | 9.2%                | 23                                             | 4                                  | 17.4% | 0                        | 0.0%  |
| 20-29 yrs | 374                          | 35                      | 9.4%                | 34                                             | 9                                  | 26.5% | 4                        | 11.8% |
| 30-39 yrs | 716                          | 82                      | 11.5%               | 77                                             | 16                                 | 20.8% | 8                        | 10.4% |
| 40-49 yrs | 645                          | 61                      | 9.5%                | 60                                             | 18                                 | 30.0% | 9                        | 15.0% |
| 50-59 yrs | 659                          | 62                      | 9.4%                | 55                                             | 13                                 | 23.6% | 8                        | 14.5% |
| 60-69 yrs | 844                          | 86                      | 10.2%               | 84                                             | 33                                 | 39.3% | 19                       | 22.6% |
| ≥70 yrs   | 547                          | 53                      | 9.7%                | 49                                             | 17                                 | 34.7% | 13                       | 26.5% |

lems in daily living”, while 68.4% of men reported the same concerns. Women were more troubled by cough than men were. Figure 5 lists the reasons given by the participants who found cough to be

“troublesome”. The most common reasons were “feeling ashamed to cough in front of other people” (49.0%), “causing trouble to other people” (42.8%) and “having difficulty in conversation” (35.5%).

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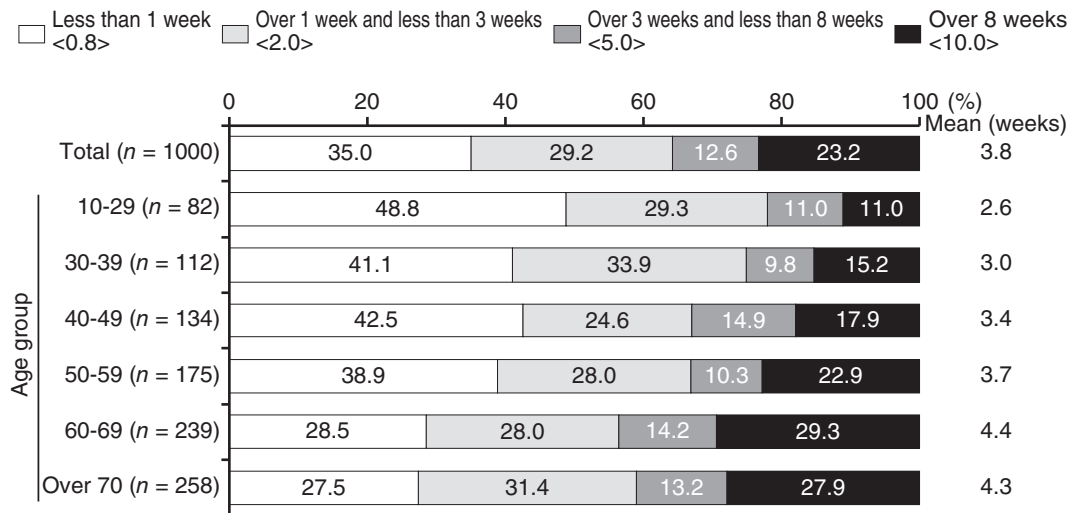


Fig. 2 Duration of cough in the surveyed population.

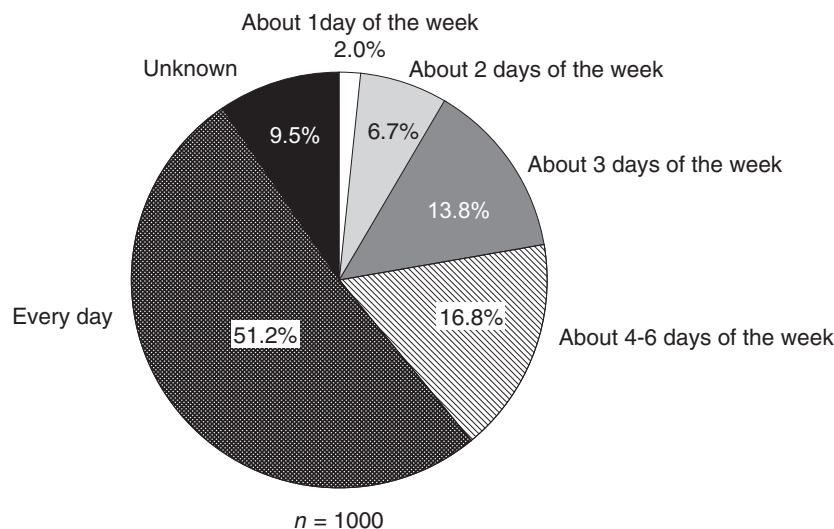


Fig. 3 Number of days in the week with cough present.

### CONSULTATION WITH A PHYSICIAN

Figure 6 shows how many participants had visited or planned to visit a medical facility in relation to their cough. In total, 440 individuals were not receiving care and did not plan to visit a medical facility. When these individuals were asked why they had not visited a medical facility, the most frequent answer was "the problem is not severe enough to necessitate a visit" (63.3%). Other common responses included "the symptom is temporary and subsides within a short while" (30.9%), "it is troublesome to visit a medical facility" (23.6%), "it is not a disease" (15.4%), "too busy to find the time to visit a medical facility" (15.0%), "healthcare costs are high" (12.4%) and "over-the-counter drugs are sufficient" (9.0%). When these individuals were asked about their medication

status, the most frequent answer was "taking no drug" (75.6%), followed by "taking over-the-counter drugs" (18.8%), "taking herbal medicines" (3.4%), and "taking food supplements" (1.8%). When the individuals taking drugs were asked about the degree of their satisfaction with the drugs being taken, 75.2% were "satisfied"/"slightly satisfied" with over-the-counter drugs, 81.0% with herbal medicines, and 54.5% with supplements.

Three-hundred and ninety-four individuals reported that they were "receiving care at present" or had "received care in the past". When these individuals were asked what triggered their visit to a medical facility, the most frequent answer was "aggravation of the symptom" (68.8%), followed by "advice from family members" (19.0%), "lack of efficacy of over-the-counter drugs" (12.2%), "advice from a physician or

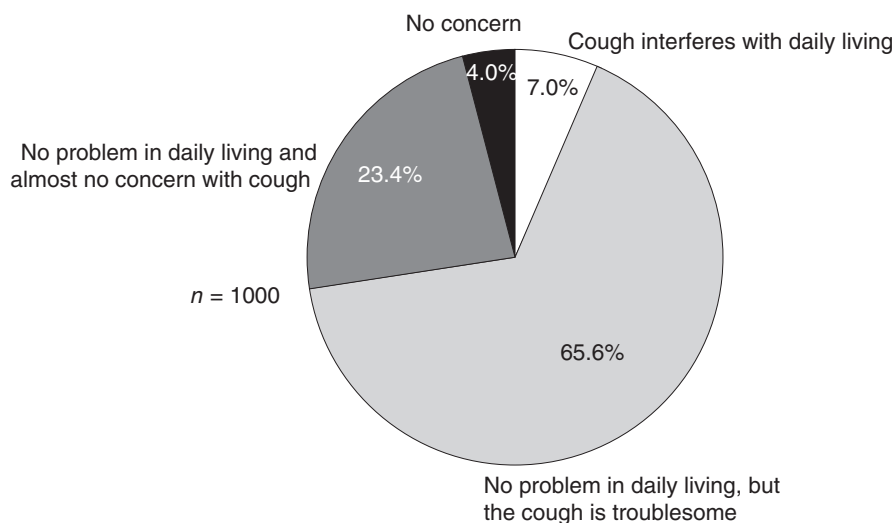


**Fig. 4** Presence/absence of problems caused by cough during daily living.

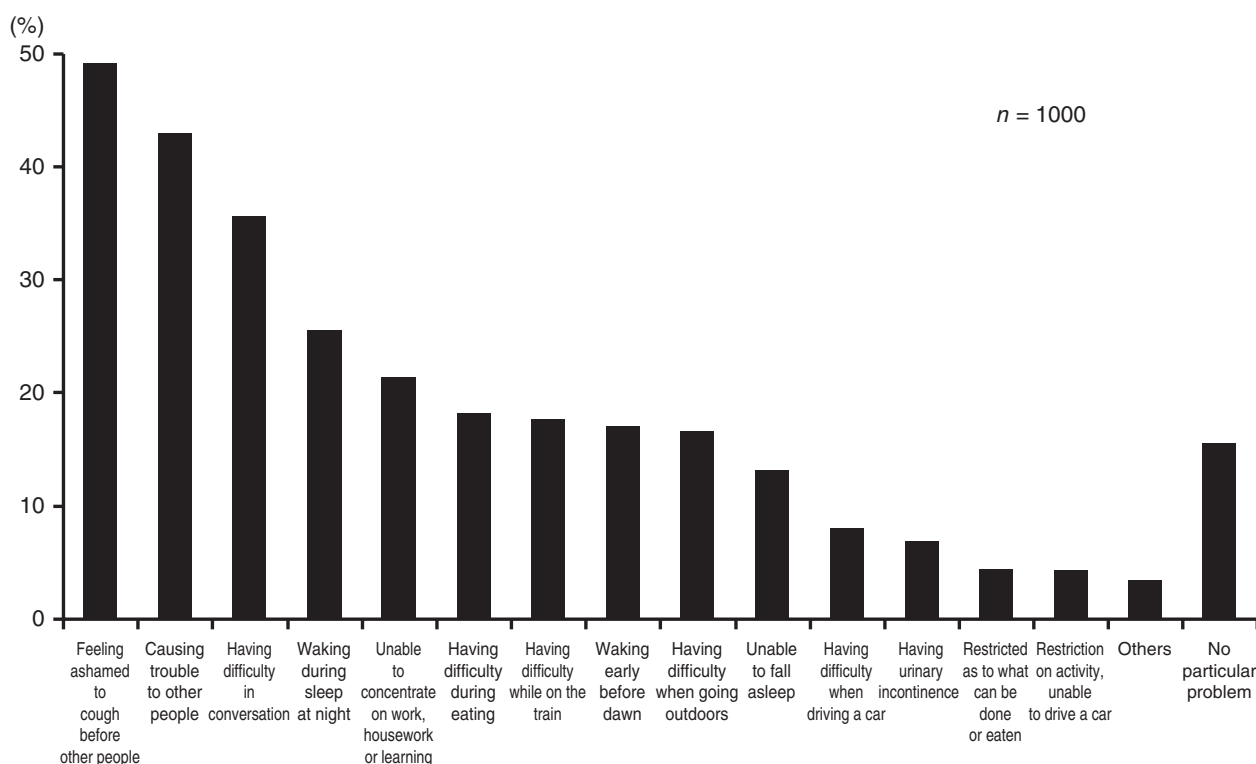


**Fig. 5** Problems caused by cough during daily living.

healthcare professional” (7.1%), and “detection of the problem during a health checkup” (4.8%). A further 166 individuals had not yet visited a facility, but planned to visit one in the future.

Compared with participants with cough lasting for <8 weeks, fewer subjects with cough lasting ≥8 weeks had not yet visited a facility and had no plans to visit one, while more subjects with cough lasting ≥8 weeks had received care in the past, but were not at the time

of survey.

#### **DISEASES CAUSING COUGH AND THE DURATION OF OUTPATIENT TREATMENT**

Overall, 68.7% of the participants wanted to identify the disease causing the cough, whereas 31.3% did not. Thus, a sizeable percentage of the individuals complaining of cough wanted to know the cause.

The diagnosed causes of cough among the 394 in-

## Survey of Persistent Cough in Japan

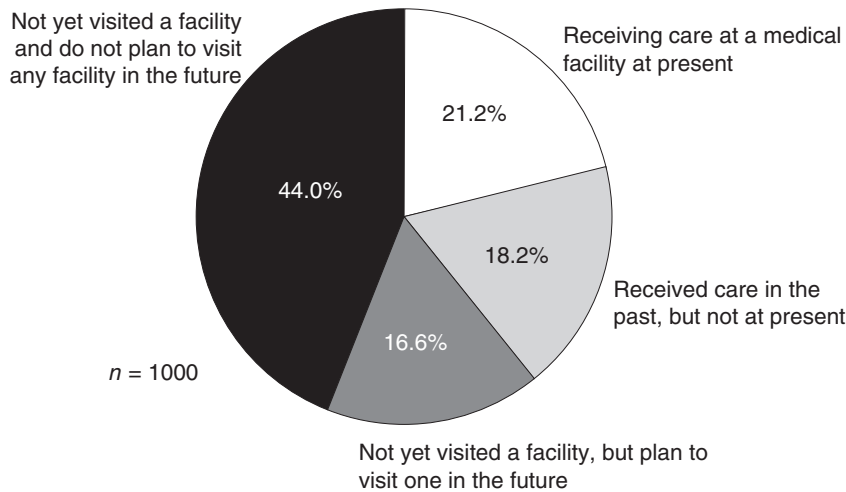


**Fig. 6** Participants' medical facility visitation status for cough treatment.

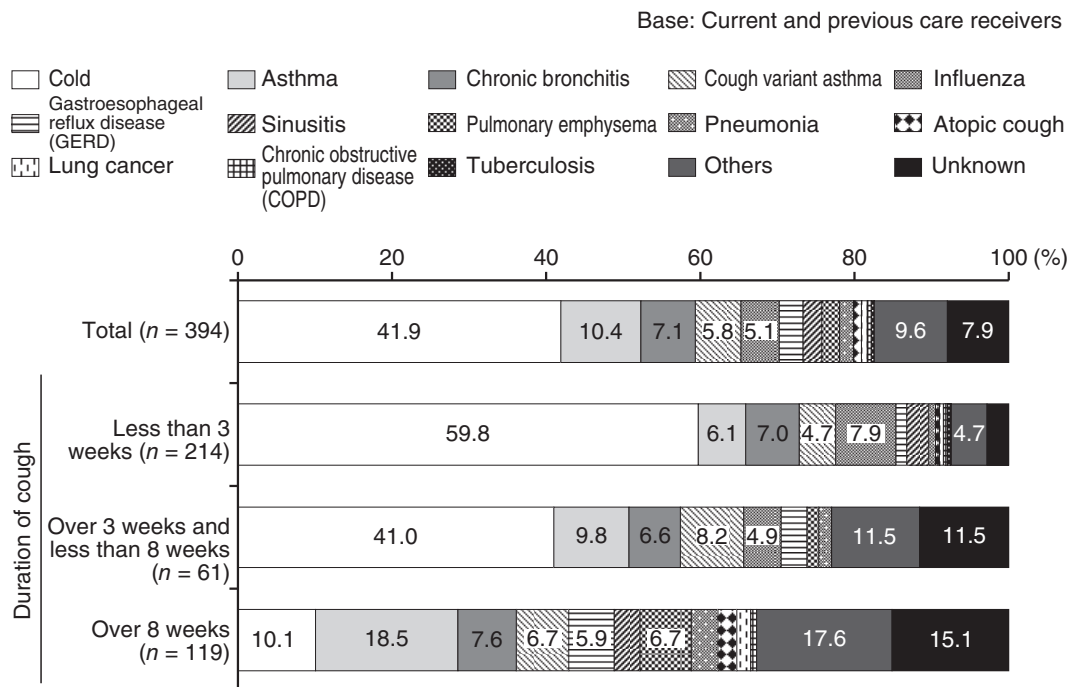


**Fig. 7** Diagnosed cause of cough among surveyed individuals who sought treatment for cough.

dividuals who reported visiting a medical facility for cough are shown in Figure 7. The most frequent diagnosis was “cold” (41.9%), followed by “asthma” (10.4%), “chronic bronchitis” (7.1%) and “cough-variant asthma” (5.8%) (Fig. 7). The percentage of individuals diagnosed with a cold became lower as the duration of cough became longer. Among individuals with cough lasting  $\geq 8$  weeks, the most frequent cause was asthma (18.5%); in 15.1% of these individuals, the diagnosis was “unidentified”.

When asked about the duration of medical care for cough, the response was “<1 week” in 37.7% of the

participants, “from 1 week to 1 month” in 24.5%, “from 1 to 3 months” in 8.0%, and “ $\geq 3$  months” in 29.7%. The mean duration of medical care was 41.3 days. Among individuals currently managed at medical facilities, 95.3% were receiving prescription drugs, and 87.1% of these individuals were complying well with the dosing instructions.

## DISCUSSION

The present survey is the first cohort study conducted to determine the prevalence of cough in the general population in Japan, and to examine its

causes and treatment in Japan.

Although the 29,085 subjects sent the screening survey had a 1 : 1 male-to-female ratio, the response rate for males was higher at about 61.5% (Table 2). The response rate was particularly high for elderly males. This bias in response rates may have occurred because elderly men use the Internet more often than other groups due to retirement/reduced work hours or simply because they had more time to respond to the questionnaire and were interested in health-related issues.

Although it has been reported that women have a higher frequency of cough than men,<sup>14</sup> the present study revealed no difference in the frequency of cough between men and women. However, a higher percentage of women tended to find cough “troublesome”, and were possibly more likely to consult a physician for treatment because of this.

The prevalence of cough in the surveyed population in Japan was 10.2%; this level of prevalence was consistent across age groups. By comparison, studies in Western countries have revealed a prevalence of cough of 9-33% of the total population.<sup>2-13</sup> However, these frequencies cannot be compared directly with those identified in the present survey because the survey periods were different and because a number of previous surveys were limited to chronic cough.

Cough lasting  $\geq 8$  weeks (chronic cough) was reported by 23.2% of the participants. On the basis of these results, we estimate that the prevalence of chronic cough is  $>2\%$  in Japan ( $>2.5$  million individuals). By comparison, the prevalence of chronic cough in Europe and the United States has been reported as 9-33%.<sup>2</sup>

Chronic cough was reported by 27.7% of men with cough and 16.0% of women with cough, the prevalence being higher in men, especially in elderly men. Factors that might be responsible for this high prevalence include the facts that men are more likely to smoke than women,<sup>15</sup> and elderly people have a longer history of smoking.

About half of all the individuals complaining of cough experienced cough every day, suggesting that cough has a considerable effect on daily living. Although only 7.0% reported that cough interfered significantly with daily living, 65.6% reported that the symptom was “troublesome”. Many of the individuals surveyed were concerned with the possibility of their cough causing discomfort for other people. Cough is thus likely to interfere with the daily living of individuals, e.g., sleep, housework and occupation. Because cough can be a sign of serious diseases such as lung cancer and pulmonary tuberculosis, individuals suffering from cough that does not resolve within a short period of time, for example, within 3 weeks, should visit a medical facility, regardless of the severity.

It is of concern that only 21.2% of individuals with

cough had visited medical facilities. Furthermore, 44.0% of the participants did not plan to visit a medical facility. The factor that most frequently triggered the visit to a medical facility was “aggravation of the symptom”. This suggests that individuals experiencing difficulties of daily living because of cough are often reluctant to visit a medical facility before their condition worsens. Therefore, educational campaigns to encourage people with persistent/chronic cough to visit a medical facility are highly desirable.

The present survey also revealed that  $\sim 70\%$  of individuals with cough lasting  $<3$  weeks developed the cough secondary to infection (for example, cold and influenza), but that more diverse diseases were responsible for cough that persisted for longer times. Among individuals with cough persisting for  $\geq 8$  weeks, asthma was the most frequent cause (18.5% due to asthma and 6.7% due to cough-variant asthma). Chronic obstructive pulmonary disease-related conditions occurred in a total of 14.3% of surveyed individuals, including 7.6% with chronic bronchitis and 6.7% with pulmonary emphysema. Cough due to gastroesophageal reflux disease was also seen in 5.9% of the surveyed individuals, suggesting that gastrointestinal disease should be considered in the etiology of cough.

To provide appropriate treatment tailored to an individual's condition, it is necessary to make a definitive diagnosis of the disease causing the cough. It would be ideal if the treatment for chronic cough is provided after identify the cause; however, definitive diagnosis of the cause is often difficult. For example, diagnosis of lung cancer and pulmonary tuberculosis requires radiography. It is also important to check for asthma and chronic obstructive pulmonary disease, which are frequent causes of chronic cough. Even after these possible diseases are ruled out, it can still be difficult to identify the cause of cough. According to the Japanese Guidelines on Cough,<sup>1</sup> “therapeutic diagnosis with bronchodilators” is useful to distinguish between cough-variant asthma and atopic cough. The guidelines describe a diagnostic approach based on a general assessment of the frequencies of causative diseases, the specificity of the drugs used for the disease, and the presence/absence of quick responses to treatment. Cough-variant asthma or atopic cough should be considered first in cases showing dry cough, whereas sinobronchial syndrome should be considered first in cases presenting with moist cough. The onset of cough-variant asthma involves contraction of the bronchial smooth muscles, and this type of cough responds well to bronchodilators such as  $\beta_2$  stimulants. By contrast, atopic cough involves enhanced sensitivity of the cough receptor on airway superficial layers, and does not respond to bronchodilators.<sup>1</sup> Therefore, it is possible to make a diagnosis of cough-variant asthma if cough disappears or is alleviated following 1-2 weeks of treatment

with a bronchodilator.

In addition to clarification of the pathophysiology of chronic cough, it is essential to undertake extensive dissemination of the methods of differential diagnosis of the causative diseases of cough among medical facilities so that appropriate treatment of chronic cough can be facilitated. At the same time, it is also desirable to undertake extensive educational campaigns about persistent cough, so as to encourage individuals having chronic cough to visit medical facilities.

In summary, this was the first large-scale cohort study using the Internet to investigate the prevalence of cough in the general population in Japan. The study revealed a prevalence of cough of 10.2% and a prevalence of chronic cough of >2% (>2.5 million individuals).

Educational campaigns targeting individuals with chronic cough have had limited effects, and relatively few individuals with cough visit a medical facility, suggesting there are many undiagnosed patients with chronic cough. Because chronic cough can be caused by a diverse array of diseases, appropriate differential diagnosis by healthcare professionals is essential. In the differential diagnosis of chronic cough, distinction between cough-variant asthma and atopic cough is particularly difficult. Therefore, it may be advisable to consider therapeutic diagnosis as a means of differential diagnosis in such cases.

## ACKNOWLEDGEMENTS

The online survey was carried out by Abbott Japan (Tokyo, Japan), and the analysis and interpretation of the results were performed by the author.

This study was supported in part by a grant-in-aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 23591142).

## SUPPLEMENTARY MATERIALS

Supplementary Table 1 is available online.

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