BMC Public Health

RESEARCH

Open Access

Association between use of heated tobacco products and long-term respiratory effects considering smoking history: internet-based cross-sectional study in Japan

Yuki Kimura[1*] and Minoru Sugita[2]

Abstract

Background With the use of heated tobacco products (HTPs) becoming more widespread in Japan, interest in the health effects of HTP has grown. Since the majority of HTP users are former smokers, information about the user's smoking history and health status before HTP use is needed when assessing the health effects of HTP use. The limited epidemiological studies available did not consistently consider this information adequately, therefore we conducted a cross-sectional study investigating the association between HTP use and respiratory chronic diseases and symptoms.

Methods The questionnaires were sent to a research panel members in Japan via the Internet, and individuals who met the study criteria and were either current exclusive HTP users, current exclusive cigarette users or those had never used tobacco products were selected. Information about the participants' smoking history and health status before they used HTPs was obtained. The effects of participant smoking history before HTP use and the impacts on outcomes upon switching to HTP were assessed using a logistic regression model. The odds ratio (OR) for current exclusive HTP users relative to never tobacco users was calculated. The OR was calculated under two scenarios, one in which the smoking history was ignored or one in which the smoking history was considered.

Results Of the participants from whom responses to the questionnaires were obtained, 17,406 participants were included in the analysis. Almost all participating current exclusive HTP users had a history of long-term smoking (mean: 30.8 years), and the occurrence of outcomes both before and after the start using HTP was reported. The ORs, without adjustment and with adjustment for smoking history before HTP use were, 3.23 (95% CI: 1.37–7.61) and 1.85 (95% CI: 0.70–4.89) respectively in COPD, same as other outcomes.

Conclusions These results suggest that smoking history before HTP using affects the occurrence of outcomes, and underscore the importance of considering smoking history when assessing the health effect of HTP use. Since the duration of HTP use is considerably shorter than that of cigarette use at present, further research, such as follow-up surveys assessing the long-term respiratory effects of HTP use, will be necessary.

Keywords Heated tobacco product, Cross-sectional study, Smoking history, Long-term respiratory effects

*Correspondence:
Yuki Kimura
yuki.kimura@jt.com
Full list of author information is available at the end of the article

Background

Heated tobacco products (HTPs), which are products that generate aerosols by heating tobacco, have been widely used among adult smokers in Japan following their launch in 2015 [1]. With this increasing use, interest in the health effects of HTP use has emerged. Growing scientific evidence on these effects includes many reports on the analysis of the components generated in vapor, in vitro/in vivo toxicity assessments, and changes in short-term biomarkers in humans observed in clinical studies [2, 3]. According to clinical studies on vapor exposure, when a smoker switches completely from combustible cigarettes (CCs) to HTPs, biomarkers related to exposure to harmful substances have been shown to decrease markedly [3, 4]. It has been reported that, in smokers switching from CCs to HTPs, biomarkers associated with biological processes such as oxidative stress, inflammation, lipometabolism and platelet activation/coagulation (biomarkers of potential harm) are similar to biomarkers of potential harm levels in people who have never used tobacco (never tobacco users) or former tobacco users [3, 5]. On the other hand, there is cross-sectional study showing adverse respiratory effects of HTP use [6].

Although the available scientific evidence to date indicates that HTPs have the potential to reduce the risk of smoking, due to the relatively recent availability of HTPs, reports on the long-term (more than several years) health effects associated with HTP use are limited, leaving any long-term health effects unclear. To assess these effects, research with long-term follow-up cohorts will be necessary, and several more years will have to pass before these results can be obtained. Consequently, at present, only a few reports from cross-sectional studies are available. Odani et al. [6] conducted a cross-sectional study among patients with cancer scheduled for surgery and reported that Prevalence Ratio (PR) for the occurrence of airway obstruction in current exclusive HTP users relative to never tobacco users was 2.32 (95% CI: 1.54–3.49), which is comparable to the PR of current exclusive cigarette smokers (2.57). Yoshioka et al. [7] also conducted a cross-sectional study in Japan over the Internet and reported that the PR for occurrence of periodontal disease in current exclusive HTP users relative to never tobacco users was 1.43 (95% CI: 1.08–1.88).

On the other hand, like HTPs, electronic cigarettes (e-cigarettes), have been cited in public health reports [8–11] for reducing harmful substances in tobacco smoke. Since e-cigarettes have been on the market for a longer period than HTPs, more research reports on the health effects of e-cigarette use than HTPs. A relationship between e-cigarette use and chronic obstructive pulmonary disease (COPD), asthma and symptoms such as wheezing has been shown. Xie et al. [12] conducted a cross-sectional study using data from the Population Assessment of Tobacco and Health (PATH) study and reported that the odds ratio (OR) for the occurrence of COPD in current e-cigarette users relative to never tobacco users was 1.62 (95% CI: 1.28–2.04). Schneller et al. [13] reported, based on a cross-sectional study using the same PATH study data used by Xie et al., that the OR of wheezing was 1.44 (95% CI: 1.01–2.06).

While these cross-sectional studies suggest various respiratory health effects associated with the use of HTPs and e-cigarettes, the number of years since the use of HTPs or e-cigarettes use is less than that since the use of CCs. Given that most users of these products have a history of smoking [14, 15], it is likely that their smoking status and health status before the start of HTP use contribute to the occurrence of chronic diseases such as COPD [16] which took many years to develop.

Almost all studies up to the present often do not obtain sufficient information on the smoking history of HTP and e-cigarette users (such as whether they smoked before the use of HTPs or e-cigarettes, the number of years of smoking, or the number of cigarettes smoked) or on their health status before they started using HTPs or e-cigarettes (such as their history of chronic diseases or other outcomes, or the occurrence of diseases or symptoms related to the occurrence of outcomes).

Because HTPs are becoming more widely used and given that there is insufficient scientific evidence on the long-term health effects associated with their use, accumulating such evidence is important.

Thus, to investigate the effect of exclusive HTP use on chronic respiratory diseases or symptoms incidence, we conducted a survey in Japan, one of the largest markets for HTPs [17], designed to include the following information: (i) individual smoking history and health status before HTP use and (ii) the temporal order of the relationship between the occurrence of chronic respiratory diseases and symptoms, which are the main outcomes, and the start of HTP use.

Methods

Study design

This was an observational, cross-sectional survey using Internet questionnaires, conducted from 2022 to 2023 to survey the long-term health effects of HTP use. The survey design involved the comparison of a group currently exclusively using HTPs (the HTP group) and a group currently exclusively using combustible cigarettes (the CC group) with a group that had never used tobacco products (the never-user group).

The survey was administrated by the healthcare-related survey company Medilead Inc., and participants were

recruited from a large-scale survey panel operated by Cross Marketing Inc., a major survey company in Japan, which is affiliated company with Medilead Inc. This survey panel consists of approximately 5 million people and allows the collection of not only basic attribute information such as sex, age and residential area but also, information necessary for surveys, such as tobacco use status, by means of Internet questionnaires.

The duration of the survey was 3 months (from December 2022 to March 2023), and an invitation to participate in this survey was sent to all survey panel members, and those willing to participate applied. The questionnaires relating to the criteria for participation in each group (the HTP group, CC group and never-user group) and including informed consent forms provided along with written information about participation in the survey were sent to the survey panel members who applied (the screening survey). The participants who responded, met the criteria for participation in the groups and provided consent were sent the questionnaire for the main survey.

The questionnaire in this study asked about the following information: whether respiratory system diseases or symptoms were present; their time of onset, current and historical tobacco use status, factors involved in the occurrence of respiratory system diseases and symptoms (information about the attributes of participants, their medical history and their lifestyle habits). This questionnaire was developed for this study in Japanese. The English translated version of this questionnaire is shown in supplementary material 1.

Participants in each group from whom responses to the questionnaires in this survey were obtained were matched by sex and age (5-year age groups) based on the HTP group.

Participants

The general requirements for participants were to have the intention to participate in this study, to understand the content of the written information for consent in this study, to have provided consent, to be men or women aged at least 20 years at the time of obtaining consent, and to meet the following criteria for their relevant group.

(1) HTP group

Participants who habitually used HTPs for a period of at least 6 months before the survey date, and whose tobacco use status after starting habitual use of HTPs was as follows: mean monthly use of combustible cigarettes of no more than 2 cigarettes, mean monthly use of other tobacco products (products containing nicotine including e-cigarettes and smokeless tobacco) of no more than 2 times, mean monthly use of HTPs of at least 3 sticks, mean frequency of use of HTPs of at least 4 days per week, no periods of 1 month or more without using HTPs, and use of at least 100 HTP sticks by the survey date (in the case of the low-temperature type, at least 25 tobacco capsules).

(2) CC group

Participants who habitually used CCs for a period of at least 6 months before the survey date, and whose tobacco use status was as follows after starting habitual use of CCs: mean monthly use of HTPs of no more than 2 sticks, mean monthly use of other tobacco products (products containing nicotine including e-cigarettes and smokeless tobacco) of no more than 2 times, mean monthly use of CCs of at least 3 cigarettes, mean frequency of use of CCs of at least 4 days per week, no periods of 1 month or more without using CCs, and use of at least 100 CCs by the survey date.

(3) Never-user group

Participants who had no experience of habitually using tobacco products and who had used a total of fewer than 100 cigarettes (/sticks) of tobacco products by the survey date.

In addition, persons working for tobacco companies and persons related to the survey organizers were excluded from all groups.

Measures of outcome

In this study, the primary outcome was whether self-reported respiratory diseases (COPD, asthma) or symptoms (shortness of breath, wheezing, cough, phlegm, lung function abnormality) occurred. Transient symptoms such as those due to the effect of colds were not included, and the symptoms included were those that occurred chronically or repeatedly and frequently. In this study, information on the occurrence of the diseases and symptoms [18] reported to be related to smoking was obtained from the following questions, separated into occurrences before and after the start of use of the tobacco products, to confirm the temporal order of the onset time of outcomes and the start of use in current exclusive HTP users and current exclusive CC users. About diseases: "Please indicate any diseases that have been diagnosed by physician since (before) you started using heated tobacco products (combustible cigarettes)," and about symptoms: "Please indicate any symptoms that have been diagnosed

by physician or symptoms that have been noticed by you since (before) you started using heated tobacco products (combustible cigarettes)."

Information about never tobacco users was obtained with the following questions. About diseases: "Please indicate any diseases that have been diagnosed by physician since the age of 20," and about symptoms: "Please indicate any symptoms that have been diagnosed by physician or symptoms that have been noticed by you since the age of 20."

Participants were asked to select yes/no for whether they had been diagnosed with or become aware of each disease and symptom, and for those who answered yes, they were asked about the age at which they were diagnosed or became aware of the disease and symptom.

Measures of tobacco product use

In addition to the information necessary for the definitions of the HTP group and CC group in the "Participants" section (whether participants had used the tobacco products for at least 6 months, their current frequency of use, the amount used over their lifetime, and the amount of other tobacco products used), information on their tobacco use status for tobacco products they were currently using (number of years of use and amount used) was obtained with the following questions. "From what age did you start habitually smoking heated tobacco products (combustible cigarettes)?" "Please tell us the mean average daily amount of heated tobacco products (combustible cigarettes) you currently use (the number of cigarettes/sticks). If you use multiple products, please respond by giving the total number."

The following questions were asked of current exclusive HTP users who had CC use for at least 1 month before the start of HTP use, to obtain information about their CC use before the start of HTP use.

"Please tell us the age at which you started using combustible cigarettes and the age at which you last smoked them (when you switched completely to heated tobacco products)." "Please tell us the mean daily number of cigarettes you smoked when you were smoking combustible cigarettes in the past."

Confounding factors

The following factors other than tobacco use affect the occurrence of outcomes that were used in past cross-sectional studies investigating the relationship of e-cigarette or HTP use to the occurrence of outcomes (COPD [12, 19–25], asthma [12, 19, 21, 23, 26–41], wheezing [13, 35, 42–46], shortness of breath/cough/phlegm [35, 36, 44, 45], lung function abnormality [47]) and cohort study [48] investigating the relationship between smoking and COPD were used as adjustment factors in this study: age, sex, BMI, resident area population size, education level, household income, whether employed or unemployed, lifestyle habits (frequency of exercise, frequency of alcohol drinking, level of stress), and whether historical or concurrent diseases were present (diabetes, lipid abnormality, hypertension, stroke, allergic dermatitis/rhinitis, angina pectoris, coronary heart disease (CHD)). Information about passive smoking was not obtained in this study, because no statistical effect from passive smoking was observed [16, 40] in past cross-sectional studies of HTPs or e-cigarettes.

In addition to these known adjustment factors, whether outcomes recurred, whether COVID-19 infection occurred, and the Brinkman index (BI) [49], an index indicating the level of smoking, which is calculated by multiplying the number of years of smoking by the daily number of cigarettes smoked and was used to indicate CC use status before the start of HTP use in current exclusive HTP users, were also used as adjustment factors.

These variables were categorized as follows: sex (male and female), resident area population (< 50,000 people, 50,000–200,000 people, 200,000–500,000, > 500,000 people), education level (junior high school/high school/technical college graduate/professional training college graduate/junior college graduate, university/graduate college graduate), household income (< 5 million yen, 5–10 million yen, 10–16 million yen, > 16 million yen), employment or unemployment (paid employment, other), frequency of exercise (almost none, 1–3 days per month/1–2 days per week, 3–4 days per week/almost every day), frequency of alcohol drinking (does not drink, gave up/almost never drinks, 1–3 days per month/1–4 days per week, at least 5 days per week), and level of stress (low, normal, high).

Statistical analysis

First, we calculated the number and frequency value (mean and standard deviation for age and BMI) of each variable as baseline characteristics. Additionally, the intergroup bias of confounding factors was investigated using Krusal-Wallis test (analysis of variance for age and BMI). Second, we calculated years of participant's tobacco use (duration of product use, smoking before HTP use).

Third, the total incidences of the most recent outcomes as of the survey date in each participant group were tabulated. In the HTP and CC groups, outcomes were categorized by whether they occurred before or after the start of HTP or CC use, and the incidences of outcomes before

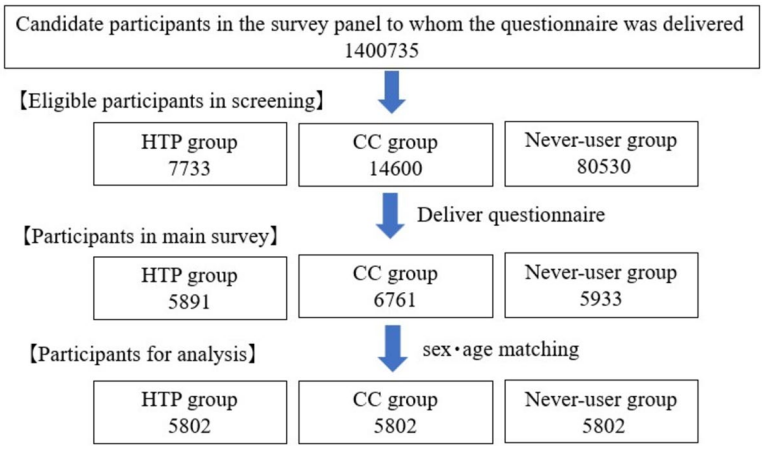

Fig. 1 Flow chart for the participants included in the study

and after the start of HTP or CC use (incidence before tobacco use, incidence after tobacco use).

If a response was obtained that stated that the same outcome was diagnosed before the most recent occurrence of the outcome as of the survey date, this was treated as the most recent occurrence of the outcome being a recurrence. In the HTP group and CC group, if an outcome was diagnosed as having occurred both before and after the start of HTP or CC use, this was treated as a recurrence of the outcome after HTP or CC use.

Forth, to analyze the effect of HTP or CC use, we performed an analysis using a logistic regression model with the occurrence of outcomes as the objective variable, smoking group and confounding factors as explanatory variables. The ORs of the HTP group and CC group relative to the never-user group were calculated.

Furthermore, to exploratively analyze the effect of the smoking experience of current exclusive HTP users before the start of HTP use on the occurrence of outcomes, the OR of the HTP group relative to the never-user group was calculated using a logistic regression model with the occurrences of outcomes after the start of HTP use, excluding occurrences of outcomes before the start of HTP use, as an objective variable. This OR was compared with the OR with the occurrences of outcomes, including outcomes before the start of HTP use, (all outcomes that occurred most recently as of the survey date) as an objective variable. In addition, to eliminate the effect from smoking before the start of HTP use, BI was added as an explanatory variable to models with the occurrences of outcomes after the start of HTP use as their objective variable. In terms of respiratory symptoms, to clarify the analysis results, we add the analysis for combined respiratory symptoms that combined the incidence of each symptom (wheezing, shortness of breath, cough, phlegm, and lung function abnormality). Since the survey uses an intergroup comparison design, with matching performed by sex and age (5-year age groups) based on the HTP group, no adjustment was made to reflect the demographics of Japan has been made.

Sensitivity analysis was performed to verify the effect of BI in the model with BI (the main analysis). The results of the main analysis were compared with the results of analysis of participants in the HTP group with no history of smoking ($n=415$). Additionally, to confirm the effect of bias associated with exclusion from randomization due to matching, similar analysis was performed for the participants before matching ($n=18{,}585$) and this was compared to the main analysis.

The data were analyzed using SAS version 9.4 (SAS Institute Japan Ltd.).

Ethical considerations

This study was conducted in accordance with the ethical guidelines for healthcare and health research in humans and was registered in the UMIN Clinical Trials Registry (UMIN000049494, registration date November 14th, 2022). Before the start of the survey, an ethics review of the survey-related documents was performed by the Institutional Review Board of Health Outcome Research Institute, and the study was approved (No. 2022-02). Web-based informed consent for participation in the survey was obtained from all participants.

Results

Number of participants

As shown in Fig. 1, the screening survey questionnaire was sent to 1,400,735 people in the registration panel of the survey company and participants who met

the inclusion criteria for each group were selected. The selected participants were sent the questionnaire for this study, and of the participants in each group from whom responses were obtained, participants in the CC group and never-user group were selected to match the sex and age (5-year age groups) in the HTP group. As a result, the incidence rates of outcomes were compared between the groups using the responses of 5,802 participants in each group.

Demographic information

The baseline characteristics are shown in Table 1. The intergroup bias was found for BMI, education, income, employment, alcohol drinking, exercise and COVID-19 infection.

HTP use behavior

The duration of tobacco use among the participants is shown in Table 2. The mean duration of HTP use in the HTP group was 3.7 years, while the mean duration of smoking (in years) before switching completely to HTPs was 30.8 years. Of the 5,802 participants in the HTP group, 415 participants responded that they had no smoking history before starting HTP use.

Incidence of outcomes

The tabulated results of incidences of the most recent outcomes as of the survey date in each participant group are shown in Table 3. For each outcome, the incidences after the start of HTP or CC use and recurrences were found. There were 57 events of COPD that occurred most recently before the survey date in the HTP group, and 35 of these, events occurred after the start of HTP use.

The ORs for the incidence of outcomes in the HTP group and CC group relative to the never-user group are shown in Table 4.

To assess the effect of HTP use on the occurrence of COPD, occurrence before the start of HTP use should be excluded, therefore the OR for occurrences after the start of HTP use (35 events) relative to occurrences in the never-user group (13 events) was calculated using a logistic regression model, and a result of 1.85 (95% CI: 0.70–4.89) was obtained. The ORs for asthma, shortness of breath, wheezing, cough, phlegm, lung function abnormalities and combined respiratory symptoms were also obtained in the same way. Tabulated results of incidences and calculated OR are shown in supplementary Tables 1,2.

The results of the sensitivity analysis are shown in Table 5. To verify the effect of BI, the same analysis as for the main analysis, the results of which are shown in Table 4, was performed for HTP users without smoking history (415 participants). These results were similar to the results for the main analysis, which included BI, and the obtained results were consistent with the effect of smoking history before HTP use on the occurrence of outcomes. (In addition, the results relative to CC group were shown in supplementary Table 3.) The results similar to those of the main analysis were also obtained from the analysis of participants before matching ($n=18,585$). (supplementary Table 4)

Discussion

Effect of smoking history before HTP use

Among the participants in this study, the mean duration of HTP use in the HTP group was 3.7 years. In addition, approximately 90% of the HTP group had CC use, and the mean duration of CC use was 30.8 years, therefore, smoking before HTP use likely contributed greatly to the occurrence of diseases and symptoms after HTP use was started. Therefore, in this survey, we obtained 2 pieces of information to adjust for the effect of smoking before HTP use in current exclusive HTP users.

The first piece of information consists of checking the incidence of outcomes that occurred before the start of HTP use (incidence before tobacco use). By differentiating this from the incidence of outcomes after HTP use (incidence after tobacco use), we removed the occurrence of outcomes before the start of HTP use, to which HTP use did not contribute. This is one of the strengths of our study, and unlike existing cross-sectional studies, the temporal relationship between the occurrence of outcomes and the start of HTP use was assessed. As a result, we found that many of the diseases and symptoms that occurred before the start of HTP use.

The second piece of information is that on the daily number of cigarettes smoked and the duration of smoking (in years) before the start of HTP use.

The results of logistic regression analysis using this information showed that, for each outcome, the OR with the incidences after the start of HTP use, excluding the incidences before the start of HTP use (incidence after tobacco use) as the objective variable, was greatly lower than the OR with the total incidence, including incidences of outcomes before the start of HTP use, as the objective variable. This finding suggested that smoking before the start of HTP use had a significant effect.

The OR of the HTP group relative to the never-user group was not statistically significant for the incidences of any outcome except phlegm, suggesting that when the duration of HTP use is short, it is difficult to confirm the effect of HTP use on the incidence of outcomes, and particularly the incidence of chronic diseases.

As another method for assessing the effect of exclusive HTP use on outcomes, we also calculated the OR of the HTP users without smoking history (415 participants)

Table 1 Demographics of the participants

Group		Never-user (*n*=5802)	HTP (*n*=5802)	CC (*n*=5802)	Total (*n*=17406)	*P*-value[*1]
Sex (n, %)	Male	4688 (80.8)	4688 (80.8)	4688 (80.8)	14064 (80.8)	1.0000
	Female	1114 (19.2)	1114 (19.2)	1114 (19.2)	3342 (19.2)	
Age (mean, SD)		51.2 (10.1)	51.3 (9.93)	51.3 (10.0)	51.3 (10.0)	0.9379
BMI (mean, SD)		23.2 (3.87)	23.3 (3.73)	23.0 (3.96)	23.1 (3.85)	< 0.0001
Resident area population (n, %)	< 50,000	763 (13.2)	608 (10.5)	687 (11.8)	2058 (11.8)	0.1293
	50,000-200,000	1489 (25.7)	1483 (25.6)	1533 (26.4)	4505 (25.9)	
	200,000-500,000	1382 (23.8)	1408 (24.3)	1341 (23.1)	4131 (23.7)	
	> 500,000	2168 (37.4)	2303 (39.7)	2241 (38.6)	6712 (38.6)	
Education (n, %)	< University/Graduate college	2392 (41.2)	2972 (51.2)	3310 (57.0)	8674 (49.8)	< 0.0001
	≥ University/Graduate college	3410 (58.8)	2830 (48.8)	2492 (43.0)	8732 (50.2)	
Income (yen/year: n, %)	< 5 million	3057 (52.7)	2403 (41.4)	3297 (56.8)	8757 (50.3)	< 0.0001
	5-10 million	1969 (33.9)	2414 (41.6)	1896 (32.7)	6279 (36.1)	
	10-16 million	596 (10.3)	802 (13.8)	486 (8.4)	1884 (10.8)	
	> 16 million	180 (3.1)	183 (3.2)	123 (2.1)	486 (2.8)	
Employment (n, %)	Employed	4511 (77.7)	4992 (86.0)	4624 (79.7)	14127 (81.2)	0.0073
	Unemployed	1291 (22.3)	810 (14.0)	1178 (20.3)	3279 (18.8)	
Alcohol drinking (n, %)	No drinking	1573 (27.1)	1073 (18.5)	1158 (20.0)	3804 (21.9)	< 0.0001
	Very seldom	1120 (19.3)	913 (15.7)	877 (15.1)	2910 (16.7)	
	Sometimes[*2]	1821 (31.4)	1547 (26.7)	1407 (24.3)	4775 (27.4)	
	Almost every day[*3]	1288 (22.2)	2269 (39.1)	2360 (40.7)	5917 (34.0)	
Exercise (n, %)	Very seldom	2752 (47.4)	3104 (53.5)	3500 (60.3)	9356 (53.8)	< 0.0001
	Sometimes[*4]	1637 (28.2)	1642 (28.3)	1283 (22.1)	4562 (26.2)	
	Almost every day[*5]	1413 (24.4)	1056 (18.2)	1019 (17.6)	3488 (20.0)	
Stress (n, %)	Low	1093 (18.8)	1113 (19.2)	1200 (20.7)	3406 (19.6)	0.2567
	Normal	2702 (46.6)	2696 (46.5)	2589 (44.6)	7987 (45.9)	
	High	2007 (34.6)	1993 (34.4)	2013 (34.7)	6013 (34.5)	
COVID-19 infection (n, %)	Infected	1109 (19.1)	1361 (23.5)	670 (11.5)	3140 (18.0)	< 0.0001
	Not infected	4693 (80.9)	4441 (76.5)	5132 (88.5)	14266 (82.0)	

Table 1 (continued)

Group		Never-user (*n*=5802)	HTP (*n*=5802)	CC (*n*=5802)	Total (*n*=17406)	*P*-value[*1]
Medical history (n, %)	Diabetes	316 (5.4)	307 (5.3)	312 (5.4)	935 (5.4)	-
	Lipid abnormality	572 (9.9)	415 (7.2)	320 (5.5)	1307 (7.5)	-
	Hypertension	1010 (17.4)	916 (15.8)	840 (14.5)	2766 (15.9)	-
	Stroke	50 (0.9)	29 (0.5)	25 (0.4)	104 (0.6)	-
	Angina pectoris	66 (1.1)	48 (0.8)	68 (1.2)	182 (1.0)	-
	Coronary heart disease	16 (0.3)	11 (0.2)	13 (0.2)	40 (0.2)	-
	Allergic dermatitis	485 (8.4)	380 (6.5)	377 (6.5)	1242 (7.1)	-
	Allergic rhinitis	1307 (22.5)	1150 (19.8)	850 (14.7)	3307 (19.0)	-

Abbreviation: *HTP* Heated Tobacco Products, *CC* Combustible Cigarettes, *BMI* Body Mass Index, *COVID* COronaVirus Infectious Disease, *SD* Standard deviation, *ANOVA* Analysis of variance

*1 ANOVA for Sex, BMI, Krusal-Wallis test for Resident area population, Education, Income, Employment, Alcohol drinking, Exercise, Stress, COVID-19 infection

*2 1-3 days/month, 1-2 days/week, 3-4 days/week

*3 5-6 days/week, every day

*4 1-3 days/month, 1-2 days/week

*5 3-4 days/week, almost every day

Table 2 Duration of product use among the participants

Group	HTP			CC		
	n	Mean	SD	n	Mean	SD
Duration of product use (year)	5802	3.70	2.37	5,802	30.5	10.4
Duration of smoking before HTP use (year)	5387	30.8	10.1	-	-	-
Duration of HTP use (participants without smoking before HTP use: year)	415	5.14	2.43	-	-	-

Abbreviation: *HTP* Heated Tobacco Products, *CC* Combustible Cigarettes, *SD* Standard Deviation

relative to the never-user group using a same model. Since responses were obtained from 5802 participants in the HTP group, the same number as in the CC group and never-user group, it was possible to obtain a subgroup of current exclusive HTP users without smoking history, which is the second strength of this study. The OR of the HTP group relative to the never-user group was similar to main analysis.

Given these our results and smoking is a risk factor for developing COPD and that it takes many years to develop [16, 50], it is considered that smoking before HTP use contributes greatly to the occurrence of COPD after the start of HTP use. Asthma and respiratory symptoms (shortness of breath, wheezing, cough, phlegm, lung function abnormality) are also related to smoking [18]. Asthma in Japanese adults occurred in all age groups [51], and the number of years until onset is vary. However, considering that chronic inflammation is involved [50], it can be considered that it takes times for asthma to develop, our results suggested that smoking before HTP use contributed greatly to the occurrence of asthma after the start of HTP use, same as COPD.

Regarding respiratory symptoms, since these symptoms occur before chronic diseases such as COPD and asthma [50], it can be considered to develop in a shorter period than chronic diseases, and the involvement of

Table 3 Number of incidences in the participant groups

Outcome	Group	Participants	Total incidence	Incidence before tobacco use	Incidence after tobacco use	Recurrence
		n	n	n	n	n
COPD	Never-user	5802	13	-	-	4
	HTP	5802	57	30	35	8
	CC	5802	47	11	46	10
Asthma	Never-user	5802	180	-	-	67
	HTP	5802	172	139	65	30
	CC	5802	181	93	121	31
Shortness of breath	Never-user	5802	306	-	-	190
	HTP	5802	318	185	192	56
	CC	5802	656	145	631	115
Wheezing	Never-user	5802	90	-	-	57
	HTP	5802	70	50	30	9
	CC	5802	133	46	111	22
Cough	Never-user	5802	665	-	-	465
	HTP	5802	461	319	218	73
	CC	5802	769	204	724	150
Phlegm	Never-user	5802	360	-	-	269
	HTP	5802	405	293	178	59
	CC	5802	793	175	767	141
Lung function abnormality	Never-user	5802	68	-	-	35
	HTP	5802	60	37	34	10
	CC	5802	80	18	71	9

Abbreviation: *HTP* Heated Tobacco Products, *CC* Combustible Cigarettes, *COPD* Chronic Obstructive Pulmonary Disease

smoking before HTP use is thought to be smaller than that of COPD and asthma. In fact, the differences in the OR with the total incidence and the OR with the incidences after the start of HTP use for each respiratory symptom were found, however the differences were not as large as those for COPD and asthma.

Comparison with reports considering the effect of smoking history

The above results suggested that to assess the relationship between HTP use and the occurrence of respiratory diseases and symptoms, considering smoking history before the start of HTP use and associated health status is important. Among the cross-sectional studies on respiratory diseases and symptoms, there are several reports relating to e-cigarettes that take into account the effect of smoking history. The cross-sectional studies of e-cigarette use in adults [20, 46] using the large-scale database BRFSS and PATH study reported a relationship between the occurrence of COPD or wheezing and e-cigarette use in current exclusive e-cigarette users without and with smoking history. In a report by Xie et al., [20] the ORs for the occurrence of COPD in current exclusive e-cigarette users without and with smoking history, were 1.47 (1.01–2.12) and 3.24 (2.78–3.78), respectively, relative to never tobacco users, suggesting that smoking history before e-cigarette use has an effect on the occurrence of COPD.

In a report by Li et al., [46] the ORs for the occurrence of wheezing (ever had wheezing or whistling in chest at any time in past) in current exclusive e-cigarette users without and with smoking history were 1.42 (0.75–2.70) and 2.27 (1.71–3.01) respectively, relative to never tobacco users. The ORs for the occurrence of separately defined wheezing (wheezing or whistling in chest in past 12 months) were 1.49 (0.84–2.67) and 2.21 (1.68–2.91) respectively, suggesting that the effect of smoking history is similar to that reported by Xie et al. [20] Studies into the effect of past smoking on asthma in adults have been reported. In a report by Parekh et al., [21] which involved a cross-sectional study of women of childbearing age (using data from the large-scale database BRFSS), the ORs for the occurrence of asthma in current exclusive e-cigarette users without and with smoking history were 1.74 (1.29–2.35) and 1.33 (0.95–1.86), respectively, relative to never tobacco users, showing that e-cigarette use had less effect on the occurrence of asthma in users with

Table 4 Results of logistic regression analysis

Outcome	Group	Total incidence		Incidence after tobacco use	
		OR[a]	95% CI	OR[b]	95% CI
COPD	Never-user	(Reference)		(Reference)	
	HTP	3.23	1.37-7.61	1.85	0.70 - 4.89
	CC	4.29	2.04-9.02	4.09	1.94 - 8.64
Asthma	Never-user	(Reference)		(Reference)	
	HTP	1.14	0.81-1.60	0.38	0.21 - 0.67
	CC	1.43	1.10-1.84	0.87	0.65 - 1.16
Shortness of breath	Never-user	(Reference)		(Reference)	
	HTP	1.95	1.46-2.60	1.22	0.86 - 1.71
	CC	5.76	4.65-7.13	5.15	4.17 - 6.37
Wheezing	Never-user	(Reference)		(Reference)	
	HTP	1.63	0.92-2.88	0.74	0.32 – 1.59
	CC	3.63	2.38-5.51	2.91	1.90 – 4.48
Cough	Never-user	(Reference)		(Reference)	
	HTP	1.55	1.23-1.96	0.94	0.69 - 1.27
	CC	3.37	2.84-4.00	3.07	2.58 – 3.65
Phlegm	Never-user	(Reference)		(Reference)	
	HTP	2.62	1.97-3.48	1.45	1.00 - 2.09
	CC	8.31	6.63-10.43	7.88	6.27 - 9.99
Lung function abnormality	Never-user	(Reference)		(Reference)	
	HTP	1.06	0.58-1.91	0.82	0.39 - 1.71
	CC	2.08	1.37-3.17	1.83	1.19 - 2.82

Abbreviation: *HTP* Heated Tobacco Products, *CC* Combustible Cigarettes, *COPD* Chronic Obstructive Pulmonary Disease, *OR* Odds Ratio, *CI* Confidence Interval, *BI* Brinkman Index

[a] (COPD) Adjusted for age, sex, education, resident area, income, employment, exercise, alcohol drinking, stress, ever diagnosed with health conditions (hypertension, lipid abnormality, stroke, and diabetes), body mass index (BMI), COVID-19 infection, recurrence of COPD

(Asthma) Adjusted for age, sex, education, resident area, income, employment, stress, ever diagnosed with health conditions (atopic dermatitis, allergic rhinitis, hypertension, stroke, heart attack, coronary heart diseases (CHD), diabetes), BMI, COVID-19 infection, recurrence of asthma

(Wheezing) Adjusted for age, sex, education, income, employment, alcohol drinking, ever diagnosed with health conditions (asthma, mental health), BMI, COVID-19 infection, recurrence of breath shortness

(Shortness of breath, Cough, Phlegm) Adjusted for age, sex, education, income, employment, ever diagnosed with health conditions (asthma, allergic rhinitis, mental health), BMI, COVID-19 infection, recurrence of wheezing/cough/phlegm

(Lung function abnormality) Adjusted for age, sex, education, income, employment, COVID-19 infection, recurrence of lung function abnormality

[b] Add "BI before HTP use" to above adjustment factors

smoking history. This result cannot consistently explain the effect of past smoking on the occurrence of asthma.

Comparison with past results of cross-sectional studies of HTP use

Studies surveying the relationship between HTP use and respiratory diseases and symptoms include a cross-sectional study that surveyed the association between HTP use and airway obstruction after patients were switched from smoking (Odani et al. [6]). The PR for occurrence of airway obstruction in current exclusive HTP users relative to never tobacco users was 2.32 (95% CI: 1.54–3.49). This PR was comparable to the PR of current exclusive cigarette smokers relative to never tobacco users, 2.57 (95% CI: 2.01–3.28).

In this study, considering that 89 of the 92 current exclusive HTP users were smokers before switching to HTP, smoking history may influence the development of airway obstruction in current exclusive HTP users. The PR for the occurrence of airway obstruction of current exclusive HTP users with smoking history relative to never HTP users with smoking history was 1.42 (1.002-2.00). This PR was significantly lower compared to the PR of current exclusive cigarette smokers relative to never tobacco users, 2.57. When the data were adjusted for past smoking history, the effect of HTP use on the occurrence of airway obstruction decreased. This finding is similar to our research results.

Table 5 Results of logistic regression analysis for HTP users never used CC

Outcome	Group	Participants	Total incidence	Incidence after tobacco use	Recurrence	OR[a]	95% CI
		n	n	n	n		
COPD	Never-user	5802	13	-	4	(Reference)	
	HTP use	415	2	1	1	-[*]	-
Asthma	Never-user	5802	180	-	67	(Reference)	
	HTP use	415	10	8	4	0.66	0.65 - 0.67
Shortness of breath	Never-user	5802	306	-	190	(Reference)	
	HTP use	415	18	14	4	1.27	0.65 - 2.46
Wheezing	Never-user	5802	90	-	57	(Reference)	
	HTP use	415	5	4	1	0.87	0.85 - 0.88
Cough	Never-user	5802	665	-	465	(Reference)	
	HTP use	415	31	23	5	1.15	0.69 - 1.90
Phlegm	Never-user	5802	360	-	269	(Reference)	
	HTP use	415	13	9	1	1.19	0.57 - 2.49
Lung function abnormality	Never-user	5802	68	-	35	(Reference)	
	HTP use	415	5	2	1	0.39	0.05 - 2.91

Abbreviation: *HTP* Heated Tobacco Products, *CC* Combustible Cigarettes, *COPD* Chronic Obstructive Pulmonary Disease, *OR* Odds Ratio, *CI* Confidence Interval

[*] The number of data was too small for the analysis

[a] OR for incidence after tobacco use

(COPD) Adjusted for age, sex, education, resident area, income, employment, exercise, alcohol drinking, stress, ever diagnosed with health conditions (hypertension, lipid abnormality, stroke, and diabetes), body mass index (BMI), COVID-19 infection, recurrence of COPD

(Asthma) Adjusted for age, sex, education, resident area, income, employment, stress, ever diagnosed with health conditions (atopic dermatitis, allergic rhinitis, hypertension, stroke, heart attack, coronary heart diseases (CHD), diabetes), BMI, COVID-19 infection, recurrence of asthma

(Wheezing) Adjusted for age, sex, education, income, employment, alcohol drinking, ever diagnosed with health conditions (asthma, mental health), BMI, COVID-19 infection, recurrence of breath shortness

(Shortness of breath, Cough, Phlegm) Adjusted for age, sex, education, income, employment, ever diagnosed with health conditions (asthma, allergic rhinitis, mental health), BMI, COVID-19 infection, recurrence of wheezing/cough/phlegm

(Lung function abnormality) Adjusted for age, sex, education, income, employment, COVID-19 infection, recurrence of lung function abnormality

Limitation

Our study has several limitations. First, since this was a cross-sectional study, we cannot assess any causal relationship between HTP use and the occurrence of outcomes. However, by confirming that outcomes had occurred after HTP use and adjusting for smoking history before HTP use and whether outcomes recurred, we were able to perform a reasonable assessment of the effect of HTP use alone on the occurrence of outcomes.

Second, the endpoints of this study included retrospective endpoints involving responses about remembered past events, and since participants may not be able to respond accurately about past events, there are some limitations in terms of the accuracy of the data. However, among the incidences of outcomes, the incidences (excluding recurrences) of COPD and asthma in all participants (aged 20 years and over) were 0.54% and 2.16% respectively, and both of these incidences were slightly greater than the proportions of patients aged 20 years and over in Japan in 2020, which were 0.34% and 1.16% [51, 52], but the incidences in this survey relating to whether or not an outcome occurred can likely be guaranteed to have a certain degree of accuracy, given that experiences of occurrence over a lifetime are counted.

Third, this study is based on questionnaires using self-reporting, and information on the diagnosis of outcomes was not from medical records, and some misclassification of all information, including tobacco use status [53, 54], may be unavoidable, which may impede the assessment of causal relatedness. Fourth, since the questionnaire survey in this study was administrated via the Internet, selection bias may exist due to the use of personal computers and smartphones. Additionally, participants were selected in eligible individuals from survey panel members who were willing to apply, therefore bias due to this procedure also may exist.

Fifth, while Internet-based surveys have the advantages of being low cost and can be conducted in a short period, participants may submit only partial data and abandon the questionnaire, and it is also difficult to explain the objective of the survey [55]. Because of this, it is possible that participants may have responded without fully understanding the content of the questions.

Conclusion

Our study assessed any respiratory health effects resulting from HTP use only, excluding factors other than HTP use, for example, by using information about smoking history or occurrences of outcomes before the start of HTP use. The results showed that, when assessing the effect of HTP use on health, it is necessary to take into account information about smoking history and associated health status before the start of HTP use.

Since the duration of HTP use is considerably shorter than that of CC use at present, further research such as follow-up surveys assessing the long-term respiratory effects of HTP use and relative to exclusive continued cigarette smoking will be necessary.

Abbreviations

HTP	Heated Tobacco Products
CC	Combustible Cigarette
FDA	Food and Drug Administration
PR	Prevalence Ratio
CI	Confidence Interval
OR	Odds Ratio
e-cigarette	Electronic cigarette
COPD	Chronic Obstructive Pulmonary Disease
BMI	Body Mass Index
CHD	Coronary Heart Diseases
BI	Brinkman Index
PATH	The Population Assessment of Tobacco and Health
BRFFS	Behavioral Risk Factor Surveillance System

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-024-20257-7.

Supplementary Material 1.

Supplementary Material 2.

Acknowledgements

We thank Medilead (https://www.medi-l.com/) for operating this survey.

Authors' contributions

YK designed the study, conducted statistical analysis and interpreted the results and wrote the first draft of the manuscript. MS contributed to the technical guidance and results discussion. All authors read and approved the final manuscript.

Funding

This work was supported by Japan Tobacco Inc. The views and conclusions contained herein are solely those of the authors and do not necessarily represent the views and conclusions of Japan Tobacco Inc.

Data availability

The datasets used during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

We obtained web-based informed consent from all participants. This study was approved by the Institutional Review Board of Health Outcome Research Institute (No. 2022-02). This study was conducted in accordance with Ethical Guidelines for Medical and Health Research Involving Human Subjects and registered at the UMIN Clinical Trials Registry (UMIN000049494).

The data were anonymized before statistical analyzes.

Consent for publication

Not applicable.

Competing interests

YK is employee of Japan Tobacco, Inc. MS have carried out consultancy work for Japan Tobacco, Inc.

Author details

[1]Scientific and Regulatory Affairs Division, Japan Tobacco Inc., Kamiyacho Trust Tower, 1-1, Toranomon 4-chome, Minato-Ku, Tokyo, Japan. [2]Toho University, 5-21-16 Omori-nishi, Ota-ku, Tokyo, Japan.

Received: 30 May 2024 Accepted: 1 October 2024
Published online: 11 October 2024

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