

# Association between heated tobacco product use and airway obstruction: a single-centre observational study, Japan

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**To cite:** Odani S, Koyama S, Miyashiro I, *et al*. Association between heated tobacco product use and airway obstruction: a single-centre observational study, Japan. *BMJ Open Respir Res* 2024;**11**:e001793. doi:10.1136/bmjresp-2023-001793

► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/bmjresp-2023-001793>).

Received 25 April 2023  
Accepted 7 February 2024



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## ABSTRACT

**Background** While heated tobacco products (HTPs) may affect pulmonary function, the evidence supporting the utility of screening for HTP use in clinical settings is insufficient. We examined the association between HTP use and airway obstruction after switching from cigarettes.

**Method** The study subjects were patients aged  $\geq 20$  years undergoing surgery from December 2021 to September 2022 who completed spirometry and reported tobacco (cigarette and HTP) use status during the preoperative assessment. Airway obstruction was defined as forced expiratory volume in 1 s to forced vital capacity ratio below the lower limit of normal. Current tobacco use was defined as past-30-day use. Multivariable Poisson regression analysis was performed to examine the associations between HTP use and airway obstruction by adjusting for demographic characteristics, lifetime cigarette smoking (pack-year) and duration of smoking cessation.

**Results** Overall (N=2850, 55.4% women, mean age 62.4), 4.6% and 10.7% reported current HTP use and cigarette smoking, respectively. 16.8% had airway obstruction. Airway obstruction was more common among current HTP-only users (adjusted prevalence ratio (APR)=2.32), current cigarette-only smokers (APR=2.57) and current dual users (APR=2.82) than never-tobacco users. Among current tobacco users (N=398), the prevalence of airway obstruction was not significantly different between HTP-only users and cigarette-only smokers. Among former cigarette smokers (>30-day cigarette quitters) (N=1077), current HTP users had 1.42 times the increased prevalence of airway obstruction than never-HTP users after adjusting for cigarette pack-year; a stronger association was observed when the analysis was restricted to  $\geq 5$ -year cigarette quitters (N=772) (APR=1.96, vs never HTP users).

**Conclusion** Current HTP use was associated with airway obstruction among patients with cancer who had completely switched from cigarettes even after quitting smoking for a long period. Patients should be routinely screened for HTP use and advised to quit any tobacco.

## INTRODUCTION

Japan is a major market for heated tobacco products (HTPs). HTPs are currently the second most used tobacco product after conventional cigarettes with an estimated 11.8% of the population using them.<sup>1</sup> In

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Heated tobacco products (HTPs), often marketed as ‘reduced-risk products’, can cause lung disease. However, the evidence supporting the utility of screening for HTP use in clinical settings is insufficient.

## WHAT THIS STUDY ADDS

⇒ Among current tobacco users, the prevalence of airway obstruction was comparable between HTP-only users and cigarette-only smokers. Among former cigarette smokers (>30-day cigarette quitters), current HTP users had a 1.42-fold increased prevalence of airway obstruction compared with never HTP users after adjusting for lifetime cigarette smoking. This was more pronounced among long-time ( $\geq 5$  years) cigarette quitters, with current HTP users having a 1.96-fold higher prevalence of airway obstruction compared with never users. Current HTP use was associated with airway obstruction after a complete switch from cigarettes.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Patients should be routinely screened for HTP use and advised to quit any tobacco. Further evaluation of the causal relationship between HTP use and lung disease is needed.

Japan, HTPs dominate as the primary novel tobacco product, while the prevalence of electronic cigarette use remains low, at below 2%.<sup>1-4</sup> This distinction is attributed to the regulatory framework that classifies electronic cigarettes as non-tobacco products and prohibits the sale of nicotine-containing e-liquids under the Pharmaceutical Affairs Law.<sup>5</sup>

While IQOS (Philip Morris International), the most popular brand of HTPs, has been approved by the US Food and Drug Administration as a ‘reduced exposure’ product, this does not necessarily translate to a reduced risk of disease.<sup>6,7</sup> There remain concerns that HTPs may lead to chronic obstructive



pulmonary disease (COPD), asthma, interstitial lung disease and cancer because they contain certain harmful constituents that are also present in conventional cigarettes.<sup>8–10</sup> In particular, COPD is one of the most common health consequences of smoking characterised by irreversible airway obstruction<sup>11</sup> and is projected to kill approximately 3 million people annually, making it the third leading cause of death by 2030.<sup>12</sup>

While studies on HTP use and pulmonary diseases are ongoing, many of them have been funded by tobacco companies<sup>13–18</sup>; the scarcity of independent evidence to validate manufacturers' data is a major challenge. A few randomised controlled trials funded by the tobacco industry have reported improvements in some biomarkers, including forced expiratory volume in 1 s (FEV<sub>1</sub>), when smokers switched to HTPs compared with those who continued to smoke cigarettes.<sup>16–18</sup> It should be stressed, however, that these findings do not imply that HTPs are harmless; evidence obtained by non-industry-related studies raises concerns regarding the short-term and long-term safety of HTPs in the respiratory system. In an anecdotal study of healthy adults, acute effects on airway function were observed after the use of IQOS that were similar to those of cigarette smoking.<sup>19</sup> An *in vitro* study has demonstrated impaired homeostasis in human airway epithelial and smooth muscle cells when they were exposed to IQOS aerosols.<sup>20</sup> Furthermore, a recent longitudinal study of a Japanese adult cohort reports that the annual decline in FEV<sub>1</sub>, a known pathological change towards obstructive pulmonary disease, was significantly greater in concurrent users of HTPs and cigarettes (–63 mL/year) than in current cigarette-only smokers (–44 mL/year).<sup>21</sup>

In clinical settings, while cigarette smoking is often screened either as a cause or an association of various health consequences, there are no clear guidelines that discuss the necessity or utility of screening for HTP use due to a lack of evidence. Given this context, our team has launched a hospital-based research project aimed at evaluating the acute and chronic health effects of HTPs in patients treated at the Osaka International Cancer Institute, the largest cancer hospital in western Japan, by linking the electronic patient records and on-site data collected through questionnaires. While data collection is ongoing, in this study, we examined the association between HTP use and airway obstruction, the hallmark of COPD, among patients undergoing tumour resection surgery. Specifically, we investigated the presence of airway obstruction among those who had switched from conventional cigarettes to HTPs including those who had long stopped cigarette smoking.

## METHODS

### Patients and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

### Study subject

From 1 December 2021 through 30 September 2022, 3080 patients scheduled for surgery at the Osaka International Cancer Institute attended a preoperative assessment by an anaesthesiologist to determine risk factors for cardiac and pulmonary complications and the patient's functional capacity. Patients who did not complete pulmonary function tests (n=195), those scheduled for surgery other than tumour resection (n=25) and individuals under 20 years old (n=10) were excluded from the study, resulting in a total of 2850 patients included in the analysis. Due to the continuous nature of data collection from all eligible patients, there was no specific target sample size. However, we have chosen to share our study's preliminary findings while data collection is still ongoing. This decision was grounded in our commitment to transparency and the timely dissemination of information.

### Data source

During the preoperative assessment, which took place an average of 11 days before the scheduled surgery date, all patients were asked to complete a questionnaire regarding tobacco use and alcohol consumption. The questionnaire was introduced at the Osaka International Cancer Institute in June 2020 as a supplement to the conventional preoperative assessment to collect detailed information on patients' lifestyle habits. Either the patients or their proxy answered the questionnaire with the assistance of trained hospital staff. The information collected through the questionnaire was stored in a database by EpiData software<sup>22</sup> and linked to information obtained from the electronic patient record system, including patient demographic and clinical information as well as the results from preoperative medical assessments. In this study, data from December 2021 onward, when pulmonary function testing was fully resumed (temporarily curtailed due to the surge of coronavirus disease 2019 (COVID-19)) were included in the analysis.

### Measures

#### Exposure: use of heated tobacco products

Tobacco product use was asked using separate questions for HTPs and cigarettes ('Select an item that applies to your [HTP use/cigarette smoking] status in the past 30 days.') with specific brand examples to reduce confusion and increase the accuracy of responses. Response items included '1. every day', '2. some days', '3a. stopped smoking cigarettes/using HTPs within the past 30 days', '3b. stopped smoking cigarettes/using HTPs more than 30 days ago' and '4. never smoked cigarettes/used HTPs'. Patients were categorised as current (past 30 days: items 1, 2 or 3a), former (item 3b) or never (item 4) HTP users or cigarette smokers. Based on this information, we further classified patients into the following mutually exclusive categories: never, former HTP-only, former cigarette-only, former dual, current HTP-only, current cigarette-only and current dual users.

### Outcome: airway obstruction

The presence of airway obstruction was defined as the ratio of FEV<sub>1</sub> to forced vital capacity (FVC) less than the lower limit of normal (LLN) derived from a representative sample of healthy individuals as recommended by the American Thoracic Society and the European Respiratory Society.<sup>23</sup> Spirometry was performed without bronchodilators by trained laboratory technicians using the FUDAC-7 spirometer (Fukuda Denshi). In Japan, airway obstruction is commonly defined in clinical practice using a fixed cut-off criterion (FEV<sub>1</sub>/FVC<0.7) according to the Global Initiative for Chronic Obstructive Lung Disease guidelines.<sup>24</sup> However, studies have shown that using a fixed threshold may lead to overdiagnosis of airway obstruction in older adults.<sup>25,26</sup> Therefore, we used the LLN derived from the Japanese spirometric reference values<sup>27</sup> to define airway obstruction (FEV<sub>1</sub>/FVC<LLN) in the main analysis; we also used a fixed ratio of 0.7 in the sensitivity analysis to examine the reproducibility of the results.

### Covariates

Covariates assessed in this study were chosen based on both data availability and their clinical relevance to the outcome, of airway obstruction. These included sex, age, cancer type, cigarette smoking, cigarette pack-year and duration of smoking cessation. Cancer types were categorised as tobacco-related cancers (cancers of the oral cavity, pharynx, larynx, oesophagus, stomach, colon and rectum, liver, pancreas, lung, kidney, bladder and cervix)<sup>28</sup> and other cancers. Cigarette pack-year, a measure of lifetime cigarette smoking predictive of lung function decline,<sup>29</sup> was calculated by multiplying the number of packs of cigarettes smoked per day by the total number of years the patient had smoked and categorised into quartiles (range 0.1–222.8, mean 32.3 (SD=27.2)). Duration of smoking cessation, a predictor associated with improved lung function and reduced risk of airway obstruction,<sup>30,31</sup> was calculated for former cigarette smokers based on their age at the time of data collection and the age and calendar month/year when they stopped smoking.

### Statistical analysis

The number and percentage of patients who currently (past 30 days) used HTPs and cigarettes and who had airway obstruction were computed. Multivariable Poisson regression models were fitted to examine the associations between the presence of airway obstruction and tobacco use status, considering former/current and exclusive/dual use of each tobacco product. Adjusted prevalence ratios (APRs) and 95% CIs for airway obstruction were calculated for the following two groups separately: all patients (with never tobacco product users as the referent) and current tobacco product users (with current cigarette-only smokers as the referent). The multivariable models were adjusted for sex, age, cancer type and lifetime cigarette smoking dose (pack-year).

To consider the temporality of tobacco product use, the associations between HTP use and airway obstruction were examined among former cigarette smokers. Multivariable models were separately fitted for former smokers overall (ie, >30-day cigarette quitters) and those who stopped smoking ≥5 years ago (≥5-year cigarette quitters) by controlling for sex, age, cancer type, cigarette pack-year and duration of cigarette smoking cessation. All analyses were performed using R V.4.1.3.

### RESULTS

**Table 1** presents the distribution of patient characteristics, HTP use, cigarette smoking and airway obstruction. Among overall patients (N=2850, 55.4% women, mean age 62.4 (SD=13.9)), 4.6% (N=132) reported current (past 30 days) HTP use and 10.7% (N=306) reported current cigarette smoking. Of the 132 current HTP users, 129 reported either past or concurrent cigarette smoking. Airway obstruction was present in 16.8% (N=480) of all patients. By HTP use status, the prevalence of airway obstruction was higher among former and current HTP users (24.7% and 22.7%, respectively) than among never users (16.3%). By cigarette smoking status, airway obstruction was present in 20.3% and 29.1% of former and current smokers, respectively, while it was observed in 11.7% of never-smokers. Along with these measures, the average FEV<sub>1</sub> and FEV<sub>1</sub>/FCV ratio stratified by sex, cancer site and other characteristics are presented in online supplemental table 1.

**Table 2** presents the association between tobacco product use and the presence of airway obstruction. Compared with those who had never used HTPs or smoked cigarettes, airway obstruction was more likely present in former and current tobacco product users with the highest likelihood in current dual users of HTPs and cigarettes (APR=2.82 (95% CI=1.61 to 4.93)), followed by current cigarette-only smokers (APR=2.57 (95% CI=2.01 to 3.28)), former dual users (APR=2.38 (95% CI=1.56 to 3.61)), current HTP-only users (APR=2.32 (95% CI=1.54 to 3.49)) and former cigarette-only smokers (APR=1.55 (95% CI=1.25 to 1.91)). Among current tobacco product users (N=398), no statistically significant differences were observed in HTP-only users and dual users, using cigarette-only smokers as the referent. A sensitivity analysis using a fixed ratio of FEV<sub>1</sub>/FVC<0.7 to define airway obstruction yielded consistent results (online supplemental table 2).

**Table 3** shows the association between HTP use and airway obstruction among former cigarette smokers. Among overall former smokers (ie, those who had stopped cigarette smoking for >30 days) (N=1077), airway obstruction was more frequently observed in those who currently used HTPs (APR=1.42 (95% CI=1.002 to 2.00)) than in those who had never used HTPs. Increased likelihoods were also seen with increasing cigarette pack-year (APR=1.71 (95% CI=1.03 to 2.83), 2.36 (95% CI=1.44 to 3.86) and 2.41 (95% CI=1.44 to 4.03) in the second, third

**Table 1** Characteristics of the study participants, tobacco product use and airway obstruction

	Distribution	Current HTP use		Current cigarette smoking		Airway obstruction	
	N (%)	N	Prevalence	N	Prevalence	N	Prevalence
Overall	2850 (100.0)	132	4.6%	306	10.7%	480	16.8%
Sex							
Men	1578 (55.4)	55	3.5%	100	6.3%	223	14.1%
Women	1272 (44.6)	77	6.1%	206	16.2%	257	20.2%
Age							
20–44	334 (11.7)	30	9.0%	43	12.9%	16	4.8%
45–54	519 (18.2)	36	6.9%	55	10.6%	54	10.4%
55–64	584 (20.5)	39	6.7%	78	13.4%	109	18.7%
65–74	826 (29.0)	21	2.5%	88	10.7%	183	22.2%
75+	587 (20.6)	6	1.0%	42	7.2%	118	20.1%
Cancer type							
Smoking-related cancer	1923 (67.5)	91	4.7%	235	12.2%	373	19.4%
Other	927 (32.5)	41	4.4%	71	7.7%	107	11.5%
Tobacco use status							
Never	1463 (51.3)	–	–	–	–	172	11.8%
Former - HTP only	1 (0.0)	–	–	–	–	0	0.0%
Former - cigarettes only	906 (31.8)	–	–	–	–	180	19.9%
Former - dual	82 (2.9)	–	–	–	–	19	23.2%
Current - HTP only	92 (3.2)	–	–	–	–	20	21.7%
Current - cigarettes only	266 (9.3)	–	–	–	–	79	29.7%
Current - dual	40 (1.4)	–	–	–	–	10	25.0%
HTP use							
Never	2629 (92.2)	–	–	260	9.9%	428	16.3%
Former	89 (3.1)	–	–	6	6.7%	22	24.7%
Current	132 (4.6)	–	–	40	30.3%	30	22.7%
Cigarette smoking							
Never	1467 (51.5)	3	0.2%	–	–	172	11.7%
Former	1077 (37.8)	89	8.3%	–	–	219	20.3%
Current	306 (10.7)	40	13.1%	–	–	89	29.1%
Airway obstruction							
Not present	2370 (83.2)	102	4.3%	217	9.2%	–	–
Present	480 (16.8)	30	6.3%	89	18.5%	–	–

Note: Current tobacco product use was defined as past-30-day use. Airway obstruction was defined as forced expiratory volume in 1 s to forced vital capacity ratio below the lower limit of normal. Cancer type was categorised as tobacco-related cancers (cancers of the oral cavity, pharynx, larynx, oesophagus, stomach, colon and rectum, liver, pancreas, lung, kidney, bladder and cervix) and other cancers. HTP, heated tobacco product.

and fourth cigarette pack-year quartiles, respectively). Airway obstruction was less likely observed in former smokers who had stopped cigarette smoking  $\geq 5$  years ago (APR=0.64 (95% CI=0.46 to 0.89)) than in those who had stopped less than a year ago. Similarly, in patients who had stopped cigarette smoking  $\geq 5$  years ago, current HTP users were 1.96 (95% CI=1.08 to 3.57) times more likely to have airway obstruction. A sensitivity analysis using a fixed ratio of  $FEV_1/FVC < 0.7$  to define airway obstruction yielded consistent results (online supplemental table 3).

## DISCUSSION

At the time of preoperative assessment, 4.6% and 10.7% of patients reported having used HTPs and cigarettes in the past 30 days, respectively. Although the data were collected at one point during the preoperative visit, we retrospectively examined patients' tobacco use behaviour to ascertain the total exposure to cigarette smoking and the temporal sequence of tobacco product use using questions that specified the type of tobacco product used, the time of initiation and quitting and the number



**Table 2** Association between tobacco product use and airway obstruction among overall and current tobacco product users

	All patients (n=2850)						Current tobacco users (n=398)						
	Distribution			Airway obstruction			Distribution			Airway obstruction			
	N	N	Prevalence	APR (95% CI)	N	Prevalence	APR (95% CI)	N	Prevalence	APR (95% CI)	N	Prevalence	APR (95% CI)
Tobacco use status													
Never used HTP nor cigarettes	1463	172	11.8%	Ref.	-	-	-	-	-	-	-	-	-
Former - HTP only	1	0	0.0%	-	-	-	-	-	-	-	-	-	-
Former - cigarettes only	906	180	19.9%	<b>1.55 (1.25 to 1.91)</b>	-	-	-	-	-	-	-	-	-
Former - dual	82	19	23.2%	<b>2.38 (1.56 to 3.61)</b>	-	-	-	-	-	-	-	-	-
Current - HTP only	92	20	21.7%	<b>2.32 (1.54 to 3.49)</b>	92	20	21.7%	1.04 (0.68 to 1.58)					
Current - cigarettes only	266	79	29.7%	<b>2.57 (2.01 to 3.28)</b>	266	79	29.7%	Ref.					
Current - dual	40	10	25.0%	<b>2.82 (1.61 to 4.93)</b>	40	10	25.0%	1.23 (0.69 to 2.21)					
Cigarette pack-year													
Never smoked cigarettes	1467	172	11.7%	-	3	0	0.0%	-					
First quartile	275	25	9.1%	-	48	6	12.5%	Ref.					
Second quartile	290	51	17.6%	-	69	14	20.3%	1.43 (0.63 to 3.27)					
Third quartile	286	74	25.9%	-	64	19	29.7%	1.95 (0.90 to 4.22)					
Fourth quartile	293	96	32.8%	-	61	25	41.0%	2.00 (0.92 to 4.33)					
Missing	239	62	25.9%	-	153	45	29.4%	1.84 (0.90 to 3.77)					
Sex													
Men	1578	223	14.1%	1.14 (0.95 to 1.37)	141	35	24.8%	1.28 (0.91 to 1.81)					
Women	1272	257	20.2%	Ref.	257	74	28.8%	Ref.					
Age													
1-year increment	-	-	-	<b>1.03 (1.02 to 1.03)</b>	-	-	-	<b>1.04 (1.03 to 1.06)</b>					
Cancer type													
Smoking-related cancer	1923	373	19.4%	<b>1.31 (1.07 to 1.61)</b>	296	88	29.7%	1.20 (0.80 to 1.78)					
Other	927	107	11.5%	Ref.	102	21	20.6%	Ref.					

Note: Current tobacco product use was defined as past-30-day use. Airway obstruction was defined as forced expiratory volume in 1 s to forced vital capacity ratio below the lower limit of normal. Cigarette pack-year was computed by multiplying the number of packs of cigarettes smoked per day by the number of years the patient had smoked (mean 32.3, SD=27.2) and was categorised into quartiles (0.1–12.0; 12.4–27.2; 27.8–44.5; and 44.7–222.8 for first to fourth quartiles, respectively). Cancer type was categorised as tobacco-related cancers (cancers of the oral cavity, pharynx, larynx, oesophagus, stomach, colon and rectum, liver, pancreas, lung, kidney, bladder and cervix) and other cancers. **Bold type** represents statistical significance. APR, adjusted prevalence ratio; HTP, heated tobacco product; Ref., Reference.



**Table 3** Association between heated tobacco product use and airway obstruction among former cigarette smokers

	>30-day quitters (n=1077)				≥5-year quitters (n=772)				
	Distribution		Airway obstruction		Distribution		Airway obstruction		
	N	Prevalence	APR (95% CI)	N	Prevalence	APR (95% CI)	N	Prevalence	APR (95% CI)
HTP use									
Never	906	180	19.9%	Ref.	704	113	16.1%	Ref.	
Former	82	19	23.2%	1.13 (0.77 to 1.67)	32	6	18.8%	1.23 (0.60 to 2.52)	
Current	89	20	22.5%	<b>1.42 (1.002 to 2.00)</b>	36	9	25.0%	<b>1.96 (1.08 to 3.57)</b>	
Cigarette pack-year									
First quartile	239	20	8.4%	Ref.	204	18	8.8%	Ref.	
Second quartile	244	41	16.8%	<b>1.71 (1.03 to 2.83)</b>	193	25	13.0%	1.38 (0.78 to 2.46)	
Third quartile	238	61	25.6%	<b>2.36 (1.44 to 3.86)</b>	161	37	23.0%	<b>2.29 (1.32 to 3.99)</b>	
Fourth quartile	246	75	30.5%	<b>2.41 (1.44 to 4.03)</b>	145	37	25.5%	<b>2.46 (1.38 to 4.38)</b>	
Missing	110	22	20.0%	1.71 (0.93 to 3.14)	69	11	15.9%	1.57 (0.75 to 3.28)	
Duration of cessation									
>30 days (<1 year)	135	39	28.9%	Ref.	-	-	-	-	
≥1 year (<5 years)	145	43	29.7%	1.09 (0.75 to 1.57)	-	-	-	-	
≥5 years	772	128	16.6%	<b>0.64 (0.46 to 0.89)</b>	772	128	16.6%	-	
Missing	25	9	36.0%	1.35 (0.70 to 2.58)	-	-	-	-	
Sex									
Men	328	55	16.8%	1.11 (0.81 to 1.50)	214	30	14.0%	1.30 (0.85 to 1.99)	
Women	749	164	21.9%	Ref.	558	98	17.6%	Ref.	
Age									
1-year increment	-	-	-	<b>1.02 (1.01 to 1.04)</b>	-	-	-	<b>1.02 (1.001 to 1.04)</b>	
Cancer type									
Smoking-related cancer	840	181	21.5%	1.07 (0.77 to 1.47)	597	106	17.8%	1.17 (0.75 to 1.81)	
Other	237	38	16.0%	Ref.	175	22	12.6%	Ref.	

Note: Current tobacco product use was defined as past-30-day use. Airway obstruction was defined as forced expiratory volume in 1 s to forced vital capacity ratio below the lower limit of normal. Cigarette pack-year was computed by multiplying the number of packs of cigarettes smoked per day by the number of years the patient had smoked (mean 32.3, SD=27.2) and was categorised into quartiles (0.1–12.0; 12.4–27.2; 27.8–44.5; and 44.7–222.8 for first to fourth quartiles, respectively). Cancer type was categorised as tobacco-related cancers (cancers of the oral cavity, pharynx, larynx, oesophagus, stomach, colon and rectum, liver, pancreas, lung, kidney, bladder and cervix) and other cancers. **Bold type** represents statistical significance. APR, adjusted prevalence ratio; HTP, heated tobacco product; Ref., Reference.

of cigarettes smoked during lifetime. Among current tobacco product users, exclusive HTP users had a comparable prevalence of airway obstruction to that of exclusive cigarette smokers. Furthermore, current HTP use was significantly associated with an increased likelihood of airway obstruction (APR=1.42, vs never used HTPs) among former smokers (those who had stopped smoking cigarettes for >30 days); a stronger association (APR=1.96, vs never used HTPs) was observed when the analysis was restricted to long-time ( $\geq 5$  years) cigarette quitters.

In this study, there were 92 current exclusive HTP users, and the majority (N=89) of them had previously smoked cigarettes; thus, they had switched from cigarettes to HTPs at some point. Among current tobacco product users, we found that current HTP-only users were at a comparable risk of airway obstruction to those who were exclusively smoking cigarettes. This result is not in line with previous tobacco industry-related studies suggesting that a complete switch to HTP could reduce the adverse health effects of cigarettes. It should be noted, however, that the association observed in this study may be biased by unmeasured factors. For instance, some patients with previously identified lung or other health problems may have switched from cigarettes to HTPs to continue tobacco use with a product they consider to be 'healthier', which may complicate the link between HTP use and health outcome measures. Continuing follow-up and longitudinal assessment will be important to elucidate the pathway underlying the use of HTPs and the development of airway obstruction in real-world settings.

Another important finding of this study was that among former cigarette smokers, current HTP users had a significantly increased risk of airway obstruction relative to those who had never used HTPs, and this association remained consistent when the analysis was restricted to long-time cigarette quitters. This suggests that switching from cigarette smoking to HTP use may still pose a significantly higher risk of airway obstruction compared with complete tobacco abstinence. Recent reviews and experimental studies on the effects of HTPs suggest that HTPs share a common pathway to pulmonary disease with conventional cigarettes and that HTPs may not be safer than cigarettes in terms of damage to respiratory systems.<sup>13 14 19 20 32 33</sup> HTPs are often marketed as a 'cleaner alternative to cigarettes' or 'reduced risk product',<sup>34-36</sup> which has successfully shaped a health-conscious image around HTPs leading the public to underestimate the potential harm of the product.<sup>37-39</sup> Tobacco control efforts require targeted messages toward smokers and the wider public that the use of any form of tobacco is not free from harm, and thus strongly discouraged. Furthermore, a recent large-scale longitudinal analysis of Japanese adults suggests that the use of HTPs does not help current cigarette smokers quit and that HTPs even increase the risk of cigarette smoking relapse for former smokers, suggesting that HTPs should not be considered as a cessation aid.<sup>40</sup> In clinical settings, given that airway obstruction and many other tobacco-induced

diseases develop after long-lasting exposure, HTP use should be routinely screened along with conventional cigarettes and patients should be advised at any clinical visit to stop using all types of tobacco.

This study had several limitations. First, we were unable to establish the causal relationship between HTP use and airway obstruction because the data were collected at one point during the preoperative assessment. However, we retrospectively investigated patients' lifetime cigarette smoking (pack-year) and duration of smoking cessation. This allowed the analysis to consider past cigarette smoking behaviour in assessing the presence of airway obstruction, particularly among long-term cigarette quitters. Second, tobacco use status in this study was self-reported or reported by a proxy and not confirmed by serological testing, making it susceptible to misrecall, social desirability bias and misinformation provided by a proxy. However, it's essential to note that the reliability of self-reported tobacco use has been previously validated,<sup>41</sup> and we implemented measures to minimise reporting errors by offering guidance from trained hospital staff. Third, the study lacked a specific target sample size due to continuous data collection from all eligible patients. Despite this, the collected sample was deemed sufficient for reliable findings, as demonstrated by consistent results in sensitivity analyses and focused subgroup analyses on former cigarette smokers with appropriate adjustments. However, the data resulted in a small number of patients for certain tobacco use subgroups; for instance, there was only one former HTP-only user and three current HTP-only users with no history of cigarette smoking. Related to this limitation, we were unable to assess the relationship between HTP use and known smoking-related postoperative outcomes such as impaired cardiovascular function, infection, delayed or impaired wound healing, intensive care unit admission and in-hospital mortality<sup>42 43</sup> due to the paucity of such events. Fourth, being derived from cancer surgery patients at a single centre, the study is subject to potential biases and limited generalisability due to specific population selection. Caution is warranted in extrapolating findings to broader populations, considering the distinct nature of the patient with cancer population, characterised by older age and specific lifestyle factors. Continued and extended data collection involving multiple medical facilities is warranted to address these limitations.

To conclude, among patients with cancer scheduled for surgery, the prevalence of airway obstruction was comparable between current HTP-only users and cigarette-only smokers after adjusting for lifetime cigarette smoking. Current HTP use was significantly associated with an increased prevalence of airway obstruction among those who had quit cigarette smoking, and this was more evident among long-time ( $\geq 5$  years) cigarette quitters. Caution is warranted when interpreting these results due to potential differences in characteristics between current HTP users and non-users that were not adjusted for in this study. Nevertheless, our findings suggest that

HTP use can be a risk factor for airway obstruction even when individuals switch from smoking cigarettes. Further assessments to elucidate the pathways between HTP use and the development of airway obstruction and other long-term tobacco-related diseases are needed. In clinical settings, patients should be routinely screened for HTP use and advised to stop using all types of tobacco.

**Acknowledgements** We thank the staff of the Division of Anesthesiology and the Department of Medical Informatics of the Osaka International Cancer Institute for their collaboration in data collection.

**Contributors** SO designed the study, cleaned and analysed the data and drafted the manuscript. SK developed the questionnaire and led the project administration. TT designed and supervised the research project and acquired financial support for this publication. TT is the guarantor of this work and, as such, takes responsibility for the integrity of the data and the accuracy of the data analysis. HT and YO conceptualised the research project and monitored data collection. All authors contributed to the interpretation of the data and critically reviewed and revised the manuscript.

**Funding** This work was supported by the Health Labour Sciences Research Grants (no. 20FA1005, 23FA0301) and the Japan Society for the Promotion of Science KAKENHI Grant (no. 21H04856). The funders had no role in designing, conducting or reporting the study.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Consent obtained from parent(s)/guardian(s).

**Ethics approval** This study involves human participants and was approved by Research Ethics Committee of the Osaka International Cancer Institute (no. 21028). Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** No data are available. The data used in this study is not publicly available due to privacy and confidentiality concerns associated with the use of patients' data.

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