

Comparison of Publications on Heated Tobacco Products With Conventional Cigarettes and Implied Desirability of the Products According to Tobacco Industry Affiliation: A Systematic Review

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Abstract

Introduction: Heated tobacco products (HTPs) have been advertised as “reduced-harm” tobacco products compared to conventional cigarettes (CC); however, no direct evidence supporting HTPs being desirable for human health exists. A previous systematic review reported that evidence on HTPs published in 2017 or earlier was primarily drawn from industry-related papers. We aimed to investigate whether tobacco industry-affiliated studies are more likely to conclude that HTPs are more desirable than CC.

Methods: PubMed and *Ichushi-Web* were searched up to March 15, 2022, for studies on HTPs published in 2017 or after. We selected studies that assessed any measures of HTPs and CC, including secondary analyses using gray literature in English or Japanese. We excluded review articles except for a meta-analysis that met the aforementioned criteria. Data on the authors’ affiliations, grant, conflict of interest, category of research subjects, and interpretation were extracted. Research members in two groups independently assessed the papers; discrepancies were solved by discussion between the groups.

Results: Overall, 134 studies met the criteria. Eighty-seven (64.9%) of them were affiliated with the tobacco industry. Of the 134 studies, 56.3% (49/87) of the industry-affiliated studies versus 19.1% (9/47) of nonindustry-affiliated studies concluded that HTPs were more desirable than CC ($p < .01$). No study investigated clinically relevant outcomes, such as disease occurrence.

Conclusions: Publications on HTPs in the biomedical literature from January 2017 to March 2022 were dominated by tobacco industry-affiliated studies. More than half of them concluded that HTPs were more desirable than CC compared to independent studies.

Implications: Tobacco industry advertises HTPs as “reduced-harm” tobacco products compared to CC. HTP users tend to consider HTPs as alternative tobacco products less harmful than CC (ie, products for “harm reduction”). Our results demonstrated that papers written by tobacco industry-affiliated authors concluded that HTPs were more desirable than CC compared to papers by independent authors. However, all their judgments were based on surrogate outcomes. Surrogate outcomes are not necessarily linked to clinically relevant outcomes such as disease occurrence. Further studies on HTPs using clinically relevant outcomes are warranted by independent authors from tobacco industry.

Introduction

Heated tobacco products (HTPs) are electric devices that heat tobacco leaves to produce aerosols for inhalation by a consumer.¹ Since this noncombustion mechanism delivers lower quantities of certain chemicals, such as tar and carbon monoxide, HTPs have been explicitly and implicitly advertised as “reduced-harm” tobacco products compared to conventional ones.^{2,3} Although the idea of a noncombustion system is not new, HTPs have been successfully marketed worldwide in recent years.^{4,5} For example, IQOS (a brand of HTP by Philip Morris International) has been on sale since 2014 in Japan and has become quite popular with more than 90% of IQOS global sales from Japan in 2016.^{6,7} In 2019, HTPs were available in more than 40 countries.⁸ HTPs have since

become popular in East Asian markets, such as South Korea and Japan, where HTPs comprised 11% (South Korea) and 23% (Japan) of national tobacco sales in 2019.⁹

In their HTP advertising, Philip Morris International¹⁰ and other tobacco companies emphasize on a large reduction in toxic and concerning substances in their products compared to conventional cigarettes (CC) using claims, such as “more than 90% reduced” and “99% off,” in Japan.^{7,11} This reduced level of exposure does not necessarily indicate a reduced risk of developing symptoms or diseases; hence, tobacco companies put a disclaimer in small letters on the package or in the advertisement stating that the stated reduced level of harmful substances does not reduce the risk compared to other products.^{7,11} Several systematic reviews reported

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that HTP aerosol had lower concentrations of toxic chemicals compared to CC; however, toxic chemicals were not completely removed from the HTP aerosol.^{12,13} Independent human-based studies indicated a potentially harmful impact of both active and passive HTP smoking on human health.^{12,13}

A systematic review on HTP use by humans found that 65% (25 out of 31) of peer-reviewed papers, published from 2010 to November 2017, were affiliated with the tobacco industry.¹⁴ Considering such results, the authors were concerned about the introduction of a possible bias favoring HTP in the literature. This systematic review, published in 2018, focused on second-hand emissions or human exposure from HTPs. However, to our knowledge, no study has focused on the interpretation of the desirability of HTPs compared to CC. With the recent rise of HTPs in the market and an increase in research interest, more literature on HTPs has been accumulated since 2017. The primary aim of the current study was to test our *a priori* hypothesis that industry-affiliated papers are more likely to conclude or imply that HTPs are “more desirable” than CC. We use the term “more desirable” to define our category because we found that some industry-affiliated studies on the aspects of HTPs were not directly associated with harm (disease or its markers) but rather with marketable factors, such as aesthetic appearance (eg, tooth color), that can be used to promote their products. This allows companies to market HTPs as more desirable than CC both explicitly and implicitly. We examined whether the type of research subjects (human, animal, *in vitro*, or physicochemical) used in HTP studies differed by affiliation status as a secondary aim because we postulated that industry-affiliated studies may tend to prefer particular study subject(s) among those four categories as they may have more research funds available than nonindustry-affiliated studies.

Methods

Literature Search Strategy and Study Selection

Between February 18 and March 15, 2022, we performed systematic searches using PubMed and *Ichushi-Web* to identify studies that assessed any measures related to HTPs and CC. *Ichushi-Web* (Igaku Chuo Zasshi) is a bibliographic database of biomedical journals published in Japan, which was established in 1903 and is updated by the Japan Medical Abstracts Society, a nonprofit organization. As HTPs became available in Japanese markets earlier than other areas or countries, more research on HTPs may have been conducted in Japan than in other areas or countries, and this research may be published in Japanese only. Therefore, we included the *Ichushi-Web* database for literature searches. Keywords for the search included general terms, such as “tobacco heating system,” “tobacco heating product,” or “heated tobacco,” and product-specific terms, such as “IQOS,” “ploom,” “glo,” “THP1.0,” or “THS2.2” (the complete search strategy is provided in Supplementary Method).

Researchers in two groups independently screened a duplicate list of candidate studies by checking the title and abstract (initial screening). Thereafter, each group identified the studies for final analysis by reading the full-text (secondary screening) according to the inclusion and exclusion criteria. For eligibility, a study had to meet all of the following four criteria: (1) an original paper published after January 2017 or later, (2) numeric outcome(s) was assessed and presented

for HTPs and for CC in a comparable fashion, (3) the study design should be experimental (including a controlled trial) to ensure comparability between HTPs and cigarette (ie, an observational study on a human subject should be excluded) if human subjects were included, and (4) a full-text of a study was written either in English or Japanese. A secondary analysis using gray literature or a meta-analysis could be included if it met all the above criteria. Studies were excluded if they met either of the following exclusion criteria: (1) a narrative review, (2) a systematic review that was not considered a meta-analysis, and (3) the primary focus of the study was on environmental pollution, such as water contamination from the waste products of cigarette or HTPs.

Ten individuals of the research members were divided into two groups (Group A: HS, NA, KY, HA, and YO, Group B: AF, YZ, BM, ST, and KS) and extracted the following three elements of each selected paper independently by the groups to Excel (Microsoft Office 2016, Microsoft Corporation, Redmond, WA, USA): (1) Subjects of the study (human, animal, *in vitro*, or physicochemical; permitting multiple categories), (2) conclusion or interpretation of the main results evaluated by authors (HTPs are more desirable, less desirable, comparable, no comment, harmful-regardless, unknown-regardless, or other), and (3) affiliation to the tobacco industry (affiliated, unaffiliated, or undetermined). Importantly, we did not assess whether the authors' conclusion or interpretation of each study was appropriately based on their results. Rather, we categorized their conclusions or interpretations into either of the seven groups based on their statement in the abstract or discussion in the main text. Notably, for the second element, we chose the word “desirable” because not all the papers discussed health-risk or safety-related outcomes; in some cases, more broader aspects of HTPs use such as aesthetic desirability, were discussed as an outcome. In addition, some authors made noncomparative statements between HTPs versus CC in their conclusion despite the presence of data on both. Therefore, we categorized these as “harmful-regardless” or “unknown-regardless. For example, “harmful-regardless” was a case where the authors concluded that HTPs were harmful to humans, despite the study results seemingly favoring HTPs over cigarettes. No papers concluded or implied “desirable-regardless.” Our judgment for the affiliation to the tobacco industry was based on the authors' affiliation(s) and stated funding source(s) or conflict of interest declaration. There were no cases categorized as “undetermined.” Details of these categorizations are shown in Table 1. Discrepancies between the two groups at each stage were solved by discussion.

Statistical Analysis

For the primary aim, we compared the proportions of studies that concluded “more desirable” by tobacco industry affiliation status using Fisher's exact test due to the relatively small sample size. We also computed the odds ratios (ORs) and their corresponding 95% confidence intervals (95% CIs) of “more desirable” conclusions in industry-affiliated studies compared to nonindustry-affiliated studies. For the secondary aim, we used the exact binomial test for each subject separately to examine whether an observed proportion of the subject of industry-affiliated studies differed from “the background proportion,” which was defined as the proportion of all the industry-affiliated studies ($n = 87$) among all studies ($n = 134$). Moreover, we calculated the Clopper and Pearson's

Table 1. Categories and Their Definitions Extracted From Each Study

1) Subjects of the study (more than one category allowed)	
Human	(1) Any biological or behavioral measures obtained from an individual human participant
Animal	(2) Any biological or other measures derived from a living animal
In vitro	(3) Biological measures obtained from in vitro experiments such as tissues or cell lines
Physicochemical	(4) Measurement of physicochemical measures or other nonbiological characteristics
2) Conclusion or interpretation made by authors considering desirability of heated tobacco product (HTP) compared to conventional cigarettes (mutually exclusive)	
More desirable	(1) Authors stated or implied that HTP is more desirable for human health than conventional cigarettes
Less desirable	(2) Authors stated or implied that HTP is less desirable for human health compared to conventional cigarettes
Comparable	(3) Authors stated or implied that desirability of HTP was comparable or similar to conventional cigarettes
No comment	(4) Authors only described results without commenting desirability of HTP
Harmful-regardless	(5) Authors stated that HTP is harmful for human health irrespective of their results
Unknown-regardless	(6) Authors stated that the effect of HTP on health is unknown irrespective of their results
Others	(7) Others
3) Affiliation to tobacco industry (mutually exclusive)	
Affiliated	(1) Affiliated with a tobacco company or protobacco organization(s)
Unaffiliated	(2) Not affiliated
Undetermined	(3) Undetermined

Behavioral measure is defined as a numeric index that quantifies any aspect of human behavior related to smoking or HTP consumption; it encompasses various measures of smoking behaviors. Examples of such measures include the frequency of smoking or HTP use per day, duration of smoking or HTP use per session, interval between smoking or HTP use, and craving for nicotine by smoking or HTP use.

exact 95% CIs. We chose this method because a global comparison by cross-tabulation (ie, 2×4 subjects, in this case) is likely to violate the assumption of “independent and identical distribution” due to overlapping counting across subjects. A p value $< .05$ was considered significant. All the analyses were performed using SAS software version 9.4 for Windows (SAS Institute Inc, Cary, NC, USA).

Ethics Approval Statement

No ethical approval was needed because publicly available data were used from previous publications.

Patient and Public Involvement

No patients or members of the public was directly involved. We collected publicly available data for secondary use from the database.

Results

We identified 1047 publications from either PubMed ($n = 833$) or Ichushi-Web ($n = 214$) without duplicates (Figure 1). We excluded 750 articles in the initial screening based on the title and abstract. We further excluded 159 articles after examining full-text in the secondary screening. We added one article upon manual search, thereby resulting in 134 articles for the final analysis (Supplementary Table 1).

Of the total 134 articles analyzed, 87 (64.9%) studies were affiliated with the tobacco industry (Table 2). Of the 134 studies, 58 (43.3%) studies concluded or implied that HTPs were more desirable than CC (Table 2). Among these 58 studies, 49 (84.5%) of them were affiliated with the tobacco

industry. When stratified by tobacco industry affiliation, 56.3% (49/87) of the industry-affiliated studies versus 19.1% (9/47) of the nonindustry-affiliated studies concluded or implied that HTPs were more desirable than CC ($p < .01$). The odds of having “more desirable” conclusions by authors from tobacco industry-affiliated studies were 5.44 times higher than nonindustry-affiliated studies (OR: 5.44, 95% CI: 2.4 to 12.6).

Physicochemical analysis was the most common study subject ($n = 59$, 37.8%), followed by in vitro (48, 30.8%), human (31, 19.9%), and animal (18, 11.5%) studies (because some studies had multiple categories, total number summed to 156, Table 3). Among the human studies, no study investigated clinically relevant outcomes, such as disease occurrence and hospital admission. No statistical difference was observed between the tobacco industry-affiliated studies and nonindustry-affiliated studies regarding each study subject (human, $p = .903$; animal, $p = .907$; in vitro, $p = .313$; physicochemical, $p = .299$, Table 3). Results with further stratification according to the study subjects and authors' conclusion by industry affiliation status are provided in Supplementary Table 2.

Discussion

This is the first systematic review that focused on the desirability of HTPs over CC stratified by the study's affiliation to the tobacco industry. Our systematic review provided several findings from the recent scientific literature on HTPs: first, among 134 studies published between January 2017 and March 2022 that met our criteria, 64.9% (84 studies)

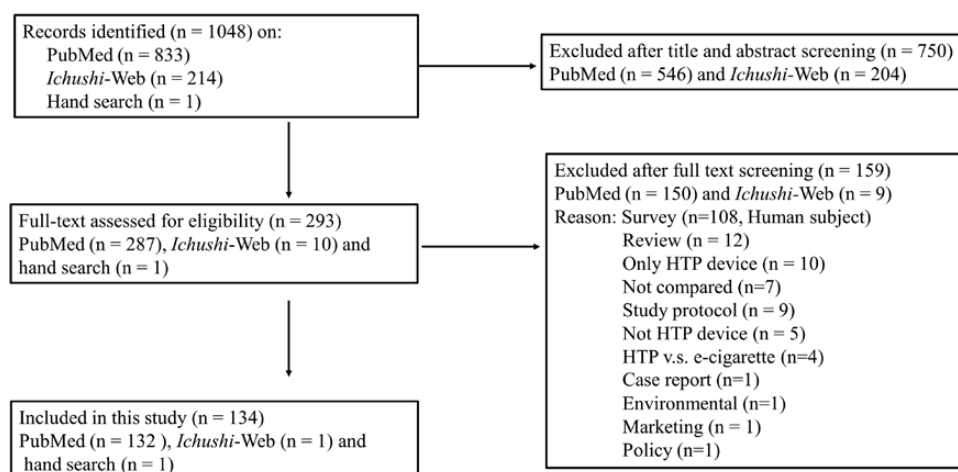


Figure 1. Publication selection flow.

Table 2. Authors' Conclusion on Desirability of Heated Tobacco Products Based on Affiliation With the Tobacco Industry

Conclusion or interpretation of the main results made by authors ^a	Affiliation to the tobacco industry		<i>p</i>	Total of number of studies, <i>n</i> (%)
	Affiliated, <i>n</i> (%)	Unaffiliated, <i>n</i> (%)		
More desirable	49 (56.3)	9 (19.1)	<.01	58 (43.3)
Less desirable	0 (0.0)	0 (0.0)	—	0 (0.0)
Comparable	1 (1.2)	11 (23.4)	—	12 (9.0)
No comment	36 (41.3)	10 (21.3)	—	46 (34.3)
Harmful-regardless	0 (0.0)	13 (27.7)	—	13 (9.7)
Unknown-regardless	1 (1.2)	4 (8.5)	—	5 (3.7)
Others	0 (0.0)	0 (0.0)	—	0 (0.0)
Number of studies	87	47		134

^a“More or less desirable,” authors stated or implied that heated tobacco product (HTP) is more or less desirable for human health than conventional cigarettes; “Comparable,” authors stated or implied that desirability of HTP was comparable or similar to conventional cigarettes; “No comment,” authors only described results without commenting on the desirability of HTP; “Harmful-regardless,” authors stated that HTP is harmful for human health irrespective of their results; “Unknown-regardless,” authors stated that the effect of HTP on health is unknown irrespective of their results. *p* value was estimated by Fisher's exact test.

Table 3. Study Subjects According to Tobacco Industry Affiliation Status

Subject of study	Number of studies on a subject, <i>n</i> ^a			Tobacco industry affiliated (%), [95% CI]	<i>p</i> ^b
	Tobacco industry		Sum		
	Unaffiliated	Affiliated			
Human	10	21	31	67.7 [48.6–83.3]	.903
Animal	7	11	18	61.1 [35.8–82.7]	.907
In vitro	13	35	48	72.9 [58.2–84.7]	.313
Physicochemical	25	34	59	57.6 [44.1–70.4]	.299
Number of studies	47†	87†	134†	64.9** (n/a)	

^aIf a paper studied multiple subjects among the four subject categories, we counted all that applied. Therefore, the total number may exceed the corresponding sum of papers (as in the bottom row, indicated by †).

^bAmong all the studies on a given subject (“number of studies on a subject, *n*”), the proportion of tobacco industry-affiliated studies on that subject was compared to the “background proportion” using the exact binomial test. “Background proportion” was defined as the proportion of all the industry-affiliated studies among all included studies (87/134 = 64.9%).

were affiliated with the tobacco industry. Second, tobacco industry-affiliated studies were more likely to conclude or imply that HTPs were more desirable than CC compared to nonaffiliated studies (56.3% in affiliated studies vs 19.1%

in nonaffiliated studies; *p* < .01). The corresponding OR [95% CI] in reference to nonaffiliated studies was 5.4 [2.4, 12.6]. Third, there was no significant difference between tobacco industry-affiliated and nonaffiliated studies regarding

the distribution of the four categories of study subjects (human, animal, in vitro, and physicochemical). With regard to the first finding (64.9% being tobacco industry-affiliated), a comparable percentage was reported by a previous systematic review¹⁴ despite the difference in the inclusion criteria from that of our study. Our findings suggest that literature on HTPs has continually been dominated by tobacco industry-affiliated papers.

Second, we found that tobacco industry-affiliated studies were more likely to conclude HTPs as more desirable, which is consistent with previous literature showing biased reporting.^{14–16} Considering these findings together, our results demonstrated that, in recent biomedical literature, tobacco industry-affiliated publications on HTPs, which favored the products they were promoting (ie, HTPs), were much more common than independent ones, suggesting potential bias in the literature. Positive advertisement on safety of HTPs would change people's perception concerning the use of HTPs.^{17,18} For example, studies from Japan, Europe, and Korea, all of which were conducted by industry-independent researchers, showed that HTP users tended to believe HTPs to be less harmful than CC.^{19–21} A previous systematic review showed that the tobacco companies have been advertising HTPs as clean, chic, and pure, a campaign aimed primarily at young people, which has increased HTP popularity among this population.²¹ The tobacco industry seems to be successful in advertising HTP as a tool for so-called “harm reduction.”¹⁷

Importantly, none of the human studies we assessed ($n = 31$) investigated clinically relevant outcomes, such as disease incidence or severity of disease symptoms. This is plausible considering that HTPs were fairly recently introduced into the market; thus, more time is warranted to assess these outcomes; however, it also meant that the implied desirability of HTPs by authors was based on nonhuman studies (Supplementary Table 1), surrogate outcomes or both.^{22–40} A surrogate outcome has been defined as a laboratory measurement or a physical sign used as a substitute for a clinically meaningful outcome that measures directly how a patient feels, functions, or survives.⁴¹ The risks of using surrogate outcomes in health risk assessment have been well described,^{41–43} as such outcomes are not necessarily linked to clinically important conditions in human beings. A great deal of uncertainty remains considering the health risk assessment of HTPs, such as whether a reduction in the toxic substances also causes a reduction in clinically adverse outcomes to the same extent. The US Food and Drug Administration approved IQOS as a modified-risk tobacco product, and permitted the marketing of the product as containing a reduced level of or presenting a reduced exposure to toxic substances. However, the product did not meet the criteria of risk modification defined by the organization, since there was no evidence demonstrating a measurable and substantial reduction in morbidity or mortality among its users.⁴⁴

In our study, 13 studies unaffiliated with the tobacco industry concluded or stated that HTPs were harmful, all of which were categorized as “harmful-regardless.” The authors of those studies seemed to focus on HTP-related harm in the absolute sense rather than making a comparative statement between HTPs and CC since HTPs contain many formerly known toxicants harmful to human beings. Additionally, a larger quantity of some substances is generated by the use of HTPs compared to the use of conventional tobacco products.⁴⁵ Such substances include propylene glycol and

glycerol⁴⁵; little is known regarding the clinical effects of inhalation of these substances on human health.^{46–48} For example, multiple cases of acute eosinophilic pneumonia related to HTP use have been reported in Japan^{49–51}; however, the exact causative agents remain to be determined. In their advertisement, tobacco companies described that their HTPs are “more than 90% reduced” or “99% free” of harmful substances compared to CC. We found a similar logic being used in some industry-affiliated studies.^{52,53} However, it is noteworthy that the reduction in disease risk is not necessarily proportional to the amount of reduction in the exposure to harmful substance. For example, a meta-analysis of 11 cohort studies reported that the pooled relative risk for coronary heart disease in men was 2.27 for 20 cigarettes per day of smoking compared to never smoking. If the risk reduction was proportional to the amount of exposure, the relative risk of one cigarette per day would have been 1.0064 with the expected excess risk being $(2.27 - 1.00)/20 \approx 0.064$. However, the observed relative risk was 1.74, which was much higher than the expected one.⁵⁴

The strength of this review is the inclusion of broad coverage of study subjects from physicochemical ones to in vitro subjects, such as animals and humans, compared with previous systematic reviews that focused only on human participants.^{14,55,56}

Caution is warranted while interpreting our results. First, we did not assess the appropriateness of the methods and results supporting the authors' conclusions in each study. Rather, we focused on the stated implications and conclusions given by the authors. Therefore, we are unable to comment on whether or not each study has biased conclusion. However, our results were consistent with the previous literature regarding the bias found in tobacco industry-affiliated studies.^{15,16} Second, the relatively small sample size limits the statistical power, although we used exact tests to address this limitation as much as possible. Third, we did not examine electronic cigarettes; thus, our findings may not be generalizable to comparisons between electronic cigarettes and conventional tobacco products.

In conclusion, publications on HTPs in the years 2017 to 2022 were dominated by tobacco industry-affiliated papers, and a significantly greater proportion of the papers (56%), as compared to the nonindustry-affiliated ones (20%), concluded or implied that HTPs were desirable than CC according to surrogate outcomes. Considering the potential bias favoring HTP, caution is warranted in appraising the current biomedical literature on HTP.

Supplementary Material

Supplementary material is available at *Nicotine and Tobacco Research* online.

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Declaration of Interests

None declared.

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Author Contributions

Harumitsu Suzuki (Conceptualization [Equal], Data curation [Equal], Formal analysis [Lead], Investigation [Equal], Project administration [Equal], Visualization [Equal], Writing—original draft [Lead], Writing—review & editing [Equal]), Naoki Aono (Investigation [Equal], Visualization [Equal], Writing—review & editing [Equal]), Yan Zhang (Data curation [Equal], Investigation [Equal], Writing—review & editing [Equal]), Kuniko Yuri (Data curation [Equal], Investigation [Equal], Writing—review & editing [Equal]), Maggy Audrey Murielle Bassole Epse Brou (Data curation [Equal], Investigation [Equal], Writing—review & editing [Equal]), Shigeki Takemura (Data curation [Equal], Investigation [Equal], Writing—review & editing [Equal]), Aya Higashiyama (Data curation [Equal], Investigation [Equal], Project administration [Equal], Supervision [Equal], Visualization [Equal], Writing—review & editing [Equal]), Takahiro Tabuchi (Conceptualization [Equal], Funding acquisition [Equal], Supervision [Equal], Writing—review & editing [Equal]), and Akira Fujiyoshi (Conceptualization [Equal], Data curation [Equal], Investigation [Equal], Project administration [Equal], Supervision [Equal], Visualization [Equal], Writing—original draft [Equal], Writing—review & editing [Equal])

Data Availability

The data underlying this article are available in the article and in its Supplementary Material. Supplementary Material shows classification of each study in this review. The code underlying this article will be available from the corresponding author upon reasonable request.

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