Modeling the Population Health Impacts of Heated Tobacco Products in Japan

Oscar M. Camacho, MSc
Andrew Hill, BSc
Stacy Fiebelkorn, MSc
Joshua D. Jones, MPharm
Krishna Prasad, PhD
Christopher Proctor, PhD
James Murphy, PhD

Objective: We evaluated the potential population health impact of launching heated tobacco products (HTP) in Japan. **Method:** We use a modeling approach to project the effects of HTP use in overall mortality up to 2100 and compare those projections against a baseline scenario based on smoking rates pre-HTP launch, ie, smoking only. The model was informed using data from publicly available sources and the literature, including population size, yearly deaths, and smoking prevalence with the initial year of 2004, and births and migration from 2004 to 2065. Transitions between products were estimated from cross-sectional population surveys in Japan. **Result:** In a worst-case scenario, population health gains would be seen with HTPs risk about 50% lower risk than smoking. Assuming equal risk for dual use and smoking, HTP risk would need to be at least 10% lower than smoking to achieve a population health benefit by 2100. Potential reduction in life-years lost with the introduction of HTPs was 13 million by 2100 compared with smoking only. **Conclusions:** In credible scenarios, substantial population harm reduction will follow the introduction of HTPs in Japan.

Key words: tobacco harm reduction; heated tobacco products; HTP; THP; population health; system dynamics model
***Tob Regul Sci.*™ 2021;7(3):221-231**
DOI: doi.org/10.18001/TRS.7.3.7

Exposure to tobacco smoke is still one of the leading preventable causes of morbidity and mortality worldwide. The implementation of tobacco control policies over the years has led to global decreases in smoking prevalence.[1] However, a large subset of the population continues to smoke, with the global number of smokers expected to reach between 1.5 billion and 2.2 billion by 2050.[2] Policies to promote smoking cessation and prevent initiation are the gold standard to reduce tobacco harm. However, smoking cessation can be a long and difficult process, and a percentage of smokers have limited desire to quit.[3] In a tobacco harm reduction framework, gains come from remaining smokers transitioning to an alternative lower risk product.[4] Around the world, various products, such as tobacco heated products (HTPs), e-cigarettes and novel nicotine pouches, are being investigated for their potential to become accepted as reduced risk products and their role in tobacco harm reduction.

HTPs comprise a heating device and consumable tobacco sticks. Instead of combusting the sticks, the device heats them enough to release nicotine, glycerol and some volatile tobacco flavor compounds in an aerosol.[5] Without combustion, the formation of many of the toxicants generated in

Oscar M. Camacho, Statistics and Modeling Manager, Scientific Research, British American Tobacco, Southampton, United Kingdom. Andrew Hill, Director, Ventana Systems United Kingdom Ltd, Salisbury, United Kingdom. Stacy Fiebelkorn, Scientist II (Data Science), Scientific Research, British American Tobacco, Southampton, United Kingdom. Joshua D. Jones, Scientist II (Consumer and Human Behavior), Scientific Research, British American Tobacco, Southampton, United Kingdom. Krishna Prasad, Consumer and Human Behavior Manager, Scientific Research, British American Tobacco, Southampton, United Kingdom. Christopher Proctor, Director, Doctor Proctor Science Ltd, Ascot, United Kingdom. James Murphy, Executive Vice President R&D and Scientific and Regulatory Affairs, R J Reynolds Tobacco Company, Winston-Salem, NC, United States. Correspondence author: Oscar M. Camacho; oscar_m_camacho@bat.com

cigarette smoke is prevented or substantially reduced,[6] translating for HTP users into substantially reduced exposure to toxicants.[7,8] A meta-analysis reviewing evidence on HTP emissions of harmful and potentially harmful constituents documented reductions of 42%-96% in experimental studies.[9] In the UK, public health authorities have stated: "There would likely be a reduction in risk for conventional smokers deciding to use heat-not-burn tobacco products instead of smoking cigarettes."[10] The US Food and Drug Administration (FDA) has stated: "Non-combusted cigarettes may help reduce the risk of tobacco-related harms for adult smokers who switch completely from combusted cigarettes, but all tobacco products can lead to nicotine addiction and contain toxic, cancer-causing chemicals that can cause serious health problems."[11]

As well as chemical characteristics, behavioral elements are important determinants of whether a product might lead to increased harm or harm reduction at the population level. Some critical aspects to consider are negative behaviors that could lead to population harm, such as the initiation of HTP use by never smokers who would not have otherwise used tobacco. Even more important, is the potential for people starting using HTPs who may then transition to smoking cigarettes, known as the gateway effect. Additionally, any benefits might be diminished by dual use – smokers adopting HTP use while continuing to smoke cigarettes – instead of switching completely to HTP use; with some reports arguing that dual use could result in greater risk than smoking alone.[12]

Smoking behaviors are highly impacted by cultural[13] and regulatory aspects. In Japan smoking prevalence is nearly 18%, remaining high compared with many other countries, and among men is nearly 30%.[14] However, Japanese consumers are open to adopting new technologies. HTPs were introduced to the Japanese market in 2014 and surveys have shown that 17.2% of men and 5.6% of women were using HTPs in 2019,[15] with approximately a ratio of 1:1 between exclusive HTP users and dual users of HTP and smoking.[16] Thus, this category is now well established, which allows estimation of prevalence and transitions between smoking and HTP use.

Epidemiological studies might not reveal the population effects of HTPs on morbidity and mortality for many decades. In the interim, computational modeling has proved to be a useful tool to evaluate long-term population effects involving tobacco products.[17] The use of such approaches has been endorsed by the FDA[18] in their Modified Risk Tobacco Product Applications draft guidance. There are now several examples of models contributing to applications assessing the population effects from launching new tobacco products.[19,20]

In this research paper, we applied a system dynamics modeling approach to assess the population health impact of launching HTPs in Japan. To inform the model we used publicly available data and transitions between products were estimated from data collected from 2 large cross-sectional surveys of smoking history and tobacco use in the previous 12 months.[16,21] We present several scenarios in which we assess the nominal risk of HTPs relative to smoking, including through initiation of HTPs by never smokers, potential reduction in cessation due to dual use and potential additional risk from dual use.

METHODS

Model Structure

We updated a previously published system dynamics model[22] to investigate the population health effects of the introduction of HTPs to Japan. The basic structure of the model was retained, and parameters were adjusted for the Japanese population instead of the UK population. The population was separated into cohorts by product use characteristics – never, current, or former smoker and, within each of these categories, never, current, or former HTP user (see supplementary information http://bit.ly/BAT_Modelling, pages 6-7). Cohorts were further partitioned by age and sex to aid alignment with the available data on births, deaths, morbidity, mortality, life expectancy, migration, and smoking prevalence (see supplementary information http://bit.ly/BAT_Modelling, page 5). Never users were defined as having used less than 100 consumables (cigarettes or HTP sticks) in their lifetime; current users as having used at least 100 consumables in their lifetime, including any use within the previous 12 months; and former users as having used more than 100 consumables in their lifetime but not in the previous 12 months.

As common terminology in this type of modeling,[23] outcomes are reported as a change of life-

Table 1
Key Input Parameters for HTP Scenarios

Input parameter	HTP scenario A	HTP scenario B	HTP scenario C
Date HTP introduced to marketplace	2015	2015	2015
Proportion of NC who would have started smoking without HTP initiation	0.5	0.5	0.5
Proportion of CC who would have started smoking without HTP initiation	0.8	0.8	0.8
Proportion of smokers who would have quit without exclusive or dual HTP use	0.1	0.1	0.1
Risk ratio of HTP compared to smoking excess risk	0.1	0.1 to 0.5	0.1 to 0.5
Combined relative risk to current or past use of both cigarettes and HTP products	Maximum	Maximum	Additive
HTP transition probabilities[a]	Weighted means	Weighted means	Weighted means

Note.
[a] Based on data in Jones et al[16] and Adamson et al.[21]
Abbreviations: HTP, heated tobacco product. NC, never smoker, current HTP user. CC, current smoker, current HTP user.

years lost which, when there are a reduction, are commonly referred as life-years saved.

Cohorts based on nicotine use status by age and gender are referred as stocks and the rates of movement of individuals between them as flows (see supplementary information http://bit.ly/BAT_Modelling, page 8), calculated once per year. Calculations were based on a first-order Markov model, where the transition flow to a different stock depends only on the current state of the source stock. The model was initiated based on data from 2004 and projections were run forward to 2100. The year 2004 was chosen as the initial year because the data source survey for smoking prevalence (Comprehensive Survey of Living Conditions) started to report in 2004 enough detail by age to inform the model.

For HTP scenarios, product introduction was at year 2015. The model was developed in Vensim DSS (a Ventana Systems product) and runs under version 8.1.

Assumptions

Where possible, data available in the public domain or obtained via 2 cross-sectional surveys were used as inputs in the model.[16,21] In the absence of data, certain assumptions were made to populate required inputs. First, the proportions of the population who initiated HTP or dual use in the previous 12 months who would have otherwise started smoking if HTPs had not been in the market were assumed to be 0.5% and 0.8%, respectively (Table 1). Second, the proportion of smokers who would have quit in the next 12 months instead of switching to HTP, or dual use if HTPs were not available, was assumed to be 0.1%. Third, the relative fraction of HTP risk to smoker risk was assumed to be 10%, based on a UK Parliament report.[24] The data behind key input parameters are provided in the supplementary information (http://bit.ly/BAT_Modelling, pages 8-30).

The model assumes that any health benefits obtained from switching to HTPs or quitting all tobacco products are lost if there is a relapse to smoking or dual use.

Scenarios

As results from scenarios are relative in nature, a hypothetical baseline scenario in which only cigarettes were available was included to allow direct assessment of changes in measures of population health after HTP launch in 2015. Three HTP scenarios were assessed based on different combinations of assumptions for product use and relative risk level of HTP compared to smoking (Table 1).

Table 2
Annual Smoking Quitting Probabilities in Japan Estimated Through Calibration

Age group (years)	Male	Female
20-29	2.2%	5.4%
30-39	3.6%	3.0%
40-49	3.9%	3.1%
50-59	4.6%	4.6%
60-69	6.9%	6.2%
70-79	9.2%	9.9%
80+	9.1%	8.5%

Calculation of Relative Risk

Current smokers were assumed to have no excess risk until age 40 years, beyond which all-cause mortality relative risks specific for age and sex were obtained from published literature [25] (see supplementary information http://bit.ly/BAT_Modelling, page 24). Each product use cohort was assigned a risk relative to that of never users of either product. Mortality was estimated from the all-cause mortality relative risk of a stock multiplied by the annual mortality proportion of never users.

Former product users retained a residual risk from previous use that declined over time according to an excess risk half-life decay time of 7.32 years.[26] If there was a relapse to smoking or dual use, we conservatively assumed that any benefit obtained from exclusive HTP use would be lost. In scenarios that involved relative risks from 2 products, either the maximum relative risk of the 2 product use statuses was used [scenarios A and B] or, the 2 excess risks were summed to provide an additive value [scenario C].

Product-specific mortality was estimated in the model using Garfinkel's method.[27] The modeled mortality rates in a given HTP or smoking scenario were compared with mortality rates if the whole population was comprised of never users. Life-years lost were calculated by multiplying age-specific and sex-specific smoking attributable deaths by life expectancy based on life tables published by the Japanese Ministry of Health, Labor and Welfare.[28]

Model Verification and Sensitivity Analysis

Standard model verification was carried out including dimensional consistency and mass balance checks. Population projections and estimated smoking prevalence were compared against published data.

All transition estimates from the cross-sectional survey provided 95% confidence limits. Transition confidence limits were used during multivariate sensitivity analysis to calculate bootstrap 95% confidence bounds over 10,000 simulations.

Univariate sensitivity testing was performed on each of the 3 model assumptions. In the absence of data to inform the sensitivity limits set for the proportion of HTP initiators who would have otherwise smoked and the proportion of smokers who would have quit instead of switching, the upper and lower bounds were set at 0 and 1. For the ratio of HTP risk to smoker relative risk, the upper and lower limits were set at 5% and 50% based on reported reductions in emissions[10] and human exposure.[9]

RESULTS

Population

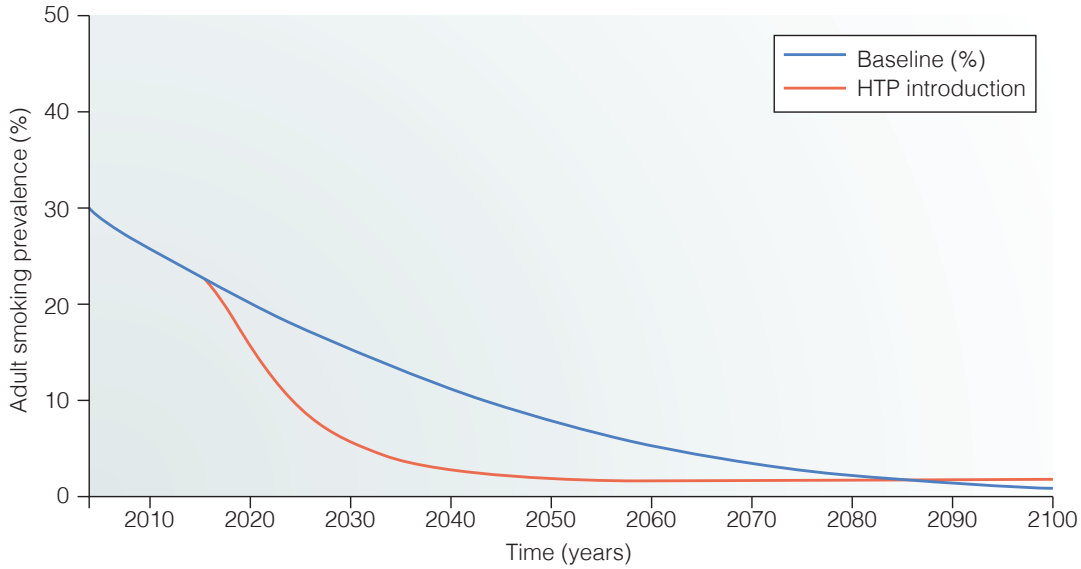
Combined surveys carried out in Japan from 2018 to 2019 yielded data from 9770 respondents.[16,21] These surveys enabled calculation of transitions rates between smoking and HTP use except for direct switching from cigarette only use to HTP only use and vice versa. All estimates for transitions can be found in the supplementary information (http://bit.ly/BAT_Modelling, pages 25-30).

In 2004, the probability of smoking initiation was estimated to be 0.581 for men and 0.246 for women at age 20 years, the legal smoking age in Japan. Based on data from the Japanese Ministry of Health, Labor and Welfare, smoking initiation probabilities had average annual decays of 4.6% and 6.7%, respectively, for men and women. Quitting probabilities were calculated based on data from the same public survey providing adjusted annual quit probabilities by age and gender (Table 2).

Scenario A

In Scenario A, the risk ratio of HTP compared to smoking excess risk was 0.1 and the combined relative risk to current or past use of both cigarettes

Figure 1
Adult Smoking Prevalence (%) Baseline (in blue) Versus HTP Introduction (Scenario A, in red) up to 2100.



and HTP products was the maximum. Overall prevalence would become similar in scenario A and the baseline scenario by 2080. However, in scenario A, the background level of smoking prevalence would be reached 30 years earlier (Figure 1).

Reduction in the number of smokers in Scenario A was coupled with an increase in HTP use, reaching a maximum of about 15% around 2030 across smoking history cohorts (Figure 2). The scenario also suggests that after an initial rise, dual use would decrease in favor of exclusive HTP use, while uptake by never smokers would surpass that in former smokers at around 2060. In scenario A, the model also indicates that the introduction of HTPs in Japan would moderate the declining trend of all tobacco products in Japan, leading to approximately 8 million users of any products by 2100, most of whom would use HTPs exclusively (Figure 2).

Smoking-related deaths converged to small rates in scenario A and the baseline scenario by 2100 as the number of smokers reduced (Figure 3). However, scenario A points to substantial reductions in life-years lost due to smoking from around 2025, resulting in roughly 13 million fewer life-years lost by 2100 (Figure 3).

In the sensitivity analysis, all projections in scenario A were positive in the study time frame, indicating between 4 million and 16 million more life-years lived than in the baseline scenario (supplementary information http://bit.ly/BAT_Modelling, Figure S2 as listed in the link).

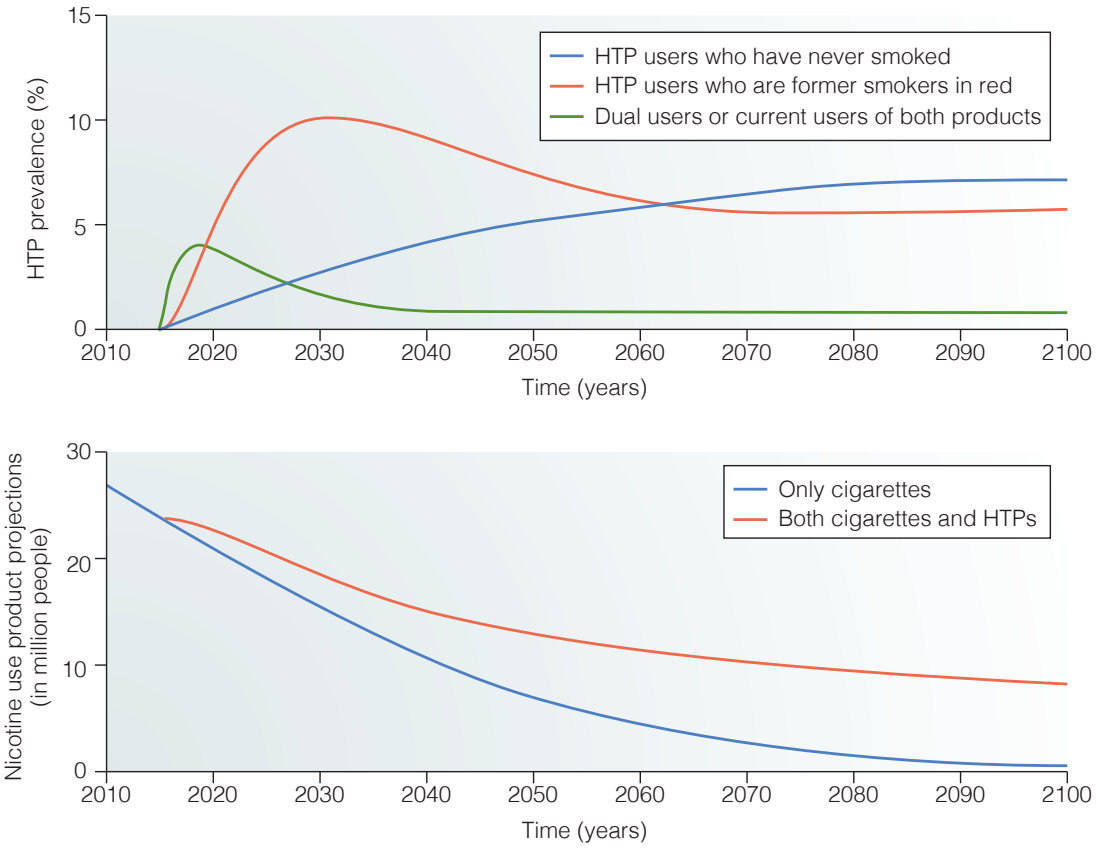
Scenario B

In Scenario B, we assessed the importance of the relative risk of using HTP with respect to smoking. The model projected a reduction in life-years lost (life-years saved) by 2100 for all credible risk levels (supplementary information http://bit.ly/BAT_Modelling, Figure S3), and a break-even level by 2100 with a risk ratio greater than 90%. After 2100, harm from HTPs would start to be predominant as smoking would have largely phased out 30-40 years earlier.

Scenario C

In a the worse-case scenario, Scenario C used additive risk to assess the health effects of dual use of

Figure 2
HTP Prevalence by Smoking Status and Overall Nicotine Use for Baseline and Scenario A

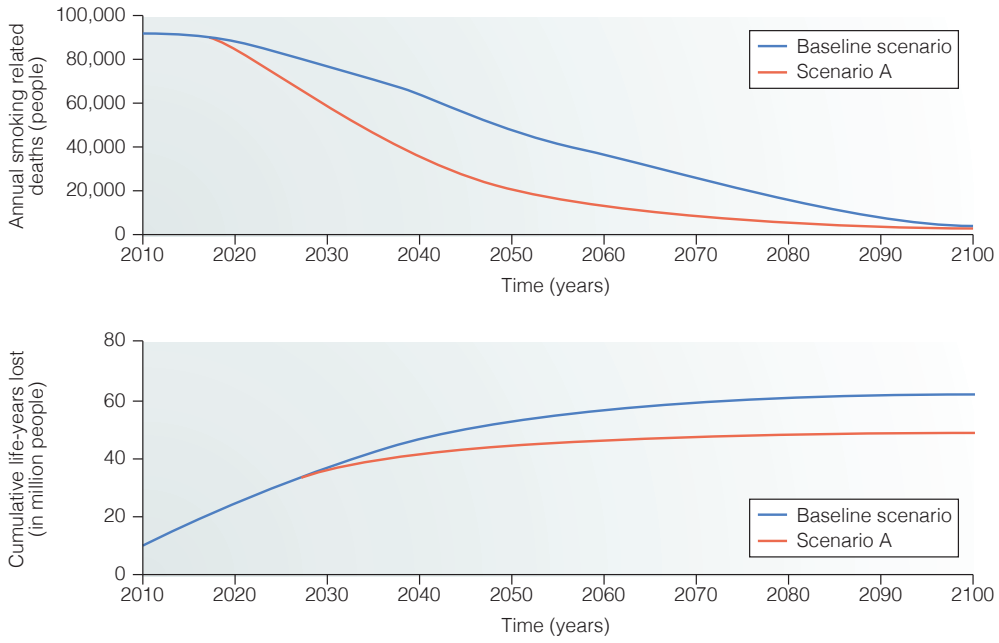


Note.
Top graph: HTP prevalence (%) by smoking status across time, with HTP users who have never smoked in blue, HTP users who are former smokers in red and, dual users or current users of both products in green. Bottom graph: nicotine use product projections overtime, with scenario with only cigarettes in blue and scenario with both, cigarettes and HTPs, in red.

HTPs and cigarettes in which the relative risk were additive, (relative risk of smoking plus a risk ratio of 0.1 for HTP use). For example, a male solus smoker of age 40 to 50 has a relative risk of 1.59. A dual user of the same gender and age, given a HTP risk ratio of 0.1 would have a relative risk of 1.649.

In an additive risk scenario, while with a risk ratio for HTP use below approximately 20%, the model suggested reductions in life-years lost for the whole run time to 2100 (supplementary information http://bit.ly/BAT_Modelling, Figure S4). The risk ratio tipping point at 2100, in which there would be no differences from the baseline scenario in terms of life-years saved or lost, was estimated to be at 49%. With risk ratios above 20% but below 49%, a net decrease would be seen in life-years lost for the first few decades while the increased risk for dual users would undermine any benefits from

Figure 3
Smoking Related Deaths and Cumulative Years Lost for Baseline and Scenario A



Note.
Top graph: annual smoking related deaths (people per year) in the baseline scenario (in blue) and scenario A (in red). Bottom graph: cumulative life-years lost (in million people per year) in the baseline scenario (in blue) and scenario A (in red).

exclusive HTP use. Later, however, as transition from dual to exclusive used increased, the model suggested overall population benefit by 2100. Beyond 2100, HTP products would need to have a risk ratio below 49% to continue to be beneficial at population level. A risk ratio of 40% in an additive scenario would reach tipping point at 2160, and the period would lengthen with decreasing size of risk ratio (supplementary information http://bit.ly/BAT_Modelling, Figure S5).

DISCUSSION

HTPs were first commercialised in Japan in 2014 and are now well-established products, by 2019, with 17.2% of men and 5.6% of women using them.[15] In addition, the fact that e-cigarettes with nicotine are banned in Japan has created a unique ecosystem to study the potential role of HTPs in a smoking harm reduction framework. Our systems dynamics modeling for Japan showed reduced mortality projections, leading to about 13 million fewer life-years lost with the introduction of HTPs by 2100 compared to the scenario where HTP have never existed.

This model was populated using publicly available data and transitions between smoking and HTP use were calculated based on a survey of 9770 participants. Our probability calculations for smoking initiation were in line with previous reports.[29,30] Our quitting probabilities are more conservative than those reported by Tabuchi et al with 3.7% to 10.7% for men and 9.9% to 16.3% for women; however, these results were estimated based on a 5-month follow-up rather than annually.[31]

The Jones et al[16] population study points to low initiation of HTP use among never smokers at 0.3%. Of these, only one (3%) transitioned from HTP into dual use and none reported transitioning

to smoking alone. These low values should mitigate concerns about potential gateway effects.

Although there is substantial literature concerning the potential effects of e-cigarettes on population health,[23,32] few data are available on the population effects of HTPs. Older-generation HTPs were not successful in the US[9] and newer generations might have been introduced too recently in the US to have attracted sufficient interest from tobacco modeling experts. A previous cohort model in Japan, performed by Lee et al,[33] suggested significantly reduced mortality. This model used an 80% risk reduction for exclusive HTP users and 40% for dual users. These findings were used in a public health impact model as part of a Modified Risk Tobacco Product Application to the FDA in the US.[34] However, the validity of the projections has been questioned, mainly because transition rates to and from HTPs in the US were speculative as the product was not commercially available in the US.[35] Of note, the model used a different structure, underlying methodology and assumptions from our analysis.

The baseline of 90% reduction in risk compared to smokers was assessed under 2 different conditions – considering the risk to be the maximum of the product exposure risk or to be additive. Following common toxicological practice, we conservatively assumed that any benefit obtained from switching would be lost if there was a relapse to smoking or dual use. In contrast with the findings of Lee et al,[33] we also considered that dual users do not gain any beneficial effect, as biomarkers of exposure in dual users have not been found to be significantly reduced compared with smokers.[36] Under the assumption that dual use is not worse than smoking, Scenario B in our model suggested that risk would have to be at least 10% lower than conventional cigarettes to start returning a population health benefit by 2100. Thus, even while considering additive risk, population benefit could be achievable if the category risk ratio to smoking turns out to be half or lower than in those who continue to smoke.

Harm reduction implies not only uptake of reduced risk products by smokers but, inevitably, initiation by never users who would otherwise have smoked. The findings from Cummings et al also seem to support this phenomenon is happening in Japan.[37] They found that since the introduction of HTPs, cigarette sales have fallen significantly faster than projected, but that the combined sales of cigarettes and HTP sticks has continued on the original tobacco consumption trajectory.

Our third assumption related to the proportion of HTP users who would have quit all tobacco products instead of switching to HTPs. We assumed that a maximum of 10% of those switching to HTP would have quit if HTPs were not available as a conservative assumption supported by literature citing quitting rates among men to be 3.7% to 10.7%, and from 9.9% to 16.3% for women.[31]

It is important to highlight that in our modeling all HTP products were considered to be homogeneous as risk estimates are not available for specific products. This could be considered a type of "halo effect"[38] which could lead to unintended consequences without appropriate regulatory and scientific assessment to ensure minimum standards across the category are met.

A limitation of the study was that all definitions were based on one-year periods, which hinders capturing direct transitions between exclusive product use as consumers appear in the model to have used both products due to defining the status of former user as having abstained for at least 12 months. Therefore, such transitions were captured by transitions to dual use and then to exclusive use. Transitions were calculated based on behaviors observed in a single year, between 2018 and 2019, and although representative of the population at that time, they do not capture variation across time. The time step in our model is one year, which means the model does not consider quit periods of up to a year, hence, our definition of a former smoker. This artifact only precludes us from including any benefits obtained from switching products for less than a year which, in terms of mortality, would be small gains.

IMPLICATIONS FOR TOBACCO REGULATION

Population data from Japan suggest that the introduction of HTPs may play an important role in tobacco harm reduction by displacing smoking without increasing overall nicotine use.[37] Displacement of cigarettes in Japan[39] would be achieved by smokers transitioning to exclusive HTP use and by

diverting those who would have smoked if HTPs were not available and who remain exclusive HTP users,[16] with only 0.3% of HTP users without a smoking history experimenting with smoking. Based on these behaviors, our model suggests that even moderate reductions in the risk of disease associated with smoking could lead to significant population health benefits. However, from a population health perspective there still remains the question of whether the Japanese phenomenon can be replicated elsewhere. With the data available, we are unable to establish with certainty whether the reduction in smoking is directly related to the category of HTPs or these changes could have been driven by societal and regulatory positions, ie, the same behavioral changes would have been observed if other alternative products, like e-cigarettes, would have been introduced in Japan instead of HTPs.

Despite societal differences, the Japanese experience may offer some value to other regulatory agencies around the world. Communication with consumers regarding the potential comparative risk between cigarette smoking and use of other smoke-free tobacco and nicotine products is a key element to persuade smokers to transition to alternatives – smoke-free tobacco and nicotine products. It has been suggested that characterizing new categories just as harmful as cigarette smoking can lead many consumers who have switched to smoking alternatives to relapse back to smoking. Additionally, adopting policies that allow for use of alternative tobacco and nicotine products in locations and areas where cigarette smoking is not permitted also can be an important factor in a smoker's decision to switch to a smoke-free tobacco and nicotine alternative.

The harm caused by smoking is undeniable and the totality of the evidence regarding HTP use establishes that smokers who completely switch to HTPs are exposed to significantly less toxicants than if they continued smoking and that reduction in toxicant exposure can be expected to reduce the risk of smoking related diseases.[24] Positive behavioral dynamics observed in the Japanese market, with many smokers switching completely to HTPs instead of continuing to smoke, would mean that even moderate reductions in risk ratio of new nicotine products compared to smoking could lead to important health benefits at the population level.

Data Availability Statement

All data used as inputs for this modeling study have been included as Supplementary Information that can be accessed via http://bit.ly/BAT_Modelling. The datasets generated during analyses are available from the corresponding author on reasonable request.

Human Subjects Approval Statement

Our study and the preparation of this paper did not involve original data collection involving human subjects.

Conflict of Interest Disclosure Statement

OMC, SF, JJ, KP, and JM are employees of British American Tobacco. This work was fully funded by British American Tobacco (Investments) Limited.

Acknowledgements

A special thanks to Claudia Kanitscheider, Ekaterina Beliaeva, Hans Bauer and Felix Marczykowski and the rest of colleagues from Kantar Germany and Kantar Japan for their invaluable contributions collecting and analysing the data used in this model.

References

1. World Health Organization (WHO). WHO global report on trends in prevalence of tobacco use 2000-2025, 3rd ed. Geneva, Switzerland: WHIO; 2019.
2. World Health Organization. Tobacco Atlas. https://www.who.int/tobacco/en/atlas38.pdf?ua=1. Accessed August 27, 2020.
3. US Department of Health and Human Services (USDHHS). *Smoking Cessation. A Report of the Surgeon General*. Atlanta, GA: USDHHS, US Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2020 https://www.hhs.gov/sites/default/files/2020-cessation-sgr-full-report.pdf. Accessed August 27, 2020.
4. Stratton K, Shetty P, Wallace R, Bondurant S. *Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction*. Washington, DC: The National Academies Press; 2001.
5. Eaton D, Blerta J, Forster M, et al. Assessment of tobacco heating product THP1.0. Part 2: product design, operation and thermophysical characterisation. *Regul Toxicol Pharmacol*. 2018;93:4-13.
6. Forster M, Fiebelkorn S, Yurteri C, et al. Assessment of novel tobacco heating product THP1.0. Part 3: comprehensive chemical characterisation of harmful and potentially harmful aerosol emissions. *Regul Toxicol Pharmacol.*

2018;93:14-33.
7. Gale N, McEwan M, Eldridge AC, et al. Changes in biomarkers of exposure on switching from a conventional cigarette to tobacco heating products: a randomized, controlled study in healthy Japanese subjects. *Nicotine Tob Res.* 2019;21:1220-1227.
8. Gale N, McEwan M, Camacho OM, et al. Changes in biomarkers of exposure on switching from a conventional cigarette to the glo tobacco heating product: a randomized, controlled ambulatory study. *Nicotine Tob Res.* 2021;23(3):584-591. doi:10.1093/ntr/ntaa135
9. Simonavicius E, McNeill A, Shahab L, Brose LS. Heat-not-burn tobacco products: a systematic literature review. *Tob Control.* 2019;28:582-594.
10. Committee on Toxicity of Chemicals in Food, Consumer Products, and the Environment (COT, COC and COM). Statement on the toxicological evaluation of novel heat-not-burn tobacco products. https://cot.food.gov.uk/sites/default/files/heat_not_burn_tobacco_statement.pdf. Published 2017. Accessed August 27, 2020.
11. US Food and Drug Administration. How are Non-Combusted Cigarettes, Sometimes Called Heat-Not-Burn Products, Different from E-cigarettes and Cigarettes? https://www.fda.gov/tobacco-products/products-ingredients-components/how-are-non-combusted-cigarettes-sometimes-called-heat-not-burn-products-different-e-cigarettes-and. Accessed February 2, 2021.
12. Wang JB, Olgin JE, Nah G, et al. Cigarette and e-cigarette dual use and risk of cardiopulmonary symptoms in the Health eHeart Study. *PLoS One.* 2018;13:e0198681.
13. Unger JB, Cruz T, Baezconde-Garbanati L, et al. Exploring the cultural context of tobacco use: a transdisciplinary framework. *Nicotine Tob Res.* 2003;5(Suppl 1):S101-S117.
14. Foundation for a Smoke-Free World. State of smoking in Japan, 2020. https://www.smokefreeworld.org/health-science-technology/health-science-technology-agenda/data-analytics/global-state-of-smoking-landscape/state-smoking-japan/. Accessed August 27, 2020.
15. Hori A, Tabuchi T, Kunugita N. Rapid increase in heated tobacco product (HTP) use from 2015 to 2019: from the Japan 'Society and New Tobacco' Internet Survey (JASTIS). *Tob Control.* 2020 Jun 5;tobaccocontrol-2020-055652. doi:10.1136/tobaccocontrol-2020-055652 [Online ahead of print]
16. Jones J, Adamson J, Kanitscheider C, et al. A national cross-sectional survey to assess tobacco and nicotine product usage patterns and behaviour since the introduction of tobacco heating products in Japan: Wave 1. *Preprints.* 2020. doi:10.20944/preprints202012.0265.v1
17. Feirman SP, Glasser AM, Rose S, et al. Computational models used to assess US tobacco control policies. *Nicotine Tob Res.* 2017;19:1257-1267.
18. US Food and Drug Administration. Center for Tobacco Products. Guidance for industry modified risk tobacco product applications. Draft guidance. March 2012. https://www.fda.gov/media/83300/download. Accessed August 27, 2020.
19. Muhammad-Kah RS, Pithawalla YB, Boone EL, et al. A computational model for assessing the population health impact of introducing a modified risk claim on an existing smokeless tobacco product. *Int J Environ Res Public Health.* 2019;16(7):1264.
20. Bachand AM, Sulsky SI. A dynamic population model for estimating all-cause mortality due to lifetime exposure history. *Regul Toxicol Pharmacol.* 2013;67:246-251.
21. Adamson J, Kanitscheider C, Prasad K, et al. Results from a 2018 cross-sectional survey in Tokyo, Osaka, and Sendai to assess tobacco and nicotine product usage after the introduction of heated tobacco products (HTPs) in Japan. *Harm Reduct J.* 2020;17:32.
22. Hill A, Camacho OM. A system dynamics modelling approach to assess the impact of launching a new nicotine product on population health outcomes. *Regul Toxicol Pharmacol.* 2017;86:265-278.
23. Lee PN, Abrams D, Bachand A, et al. Estimating the population health impact of recently introduced modified risk tobacco products: a comparison of different approaches. *Nicotine Tob Res.* 2021;23(3):426-437. doi:10.1093/ntr/ntaa102
24. UK Parliament. E-cigarettes. https://publications.parliament.uk/pa/cm201719/cmselect/cmsctech/505/50505.htm#footnote-112. Accessed August 20, 2020.
25. Murakami Y, Miura K, Okamura T, Ueshima H. EPOCH-JAPAN Research Group. Population attributable numbers and fractions of deaths due to smoking: a pooled analysis of 180,000 Japanese. *Prev Med.* 2011;52(1):60-65.
26. Fry JS, Lee PN, Forey BA, Coombs KJ. How rapidly does the excess risk of lung cancer decline following quitting smoking? A quantitative review using the negative exponential model. *Regul Toxicol Pharmacol.* 2013;67:13-26.
27. Garfinkel L. Cancer mortality in nonsmokers: prospective study by the American Cancer Society. *J Natl Cancer Inst.* 1980;65:1169-1173.
28. Ministry of Health Labor and Welfare. Life tables (MHLW, 2015). https://www.mhlw.go.jp/english/database/db-hw/lifetb15/dl/lifetb15-05.pdf. Accessed March 12, 2021.
29. Stellman SD, Takezaki T, Wang L, et al. Smoking and lung cancer risk in American and Japanese Men: an international case-control study. *Cancer Epidemiology Biomarkers Prev.* 2001;10:1193-1199.
30. Wise DA, Yashiro N. *Health Care Issues in the United States and Japan*. Chicago, IL: National Bureau of Economic Research, University of Chicago Press; 2006.
31. Tabuchi T, Nakamura M, Nakayama T, et al. Tobacco price increase and smoking cessation in Japan, a developed country with affordable tobacco: a national population-based observational study. *J Epidemiol.* 2016;26:14-21.
32. Warner KE, Mendez D. E-cigarettes: Comparing the possible risks of increasing smoking initiation with the potential benefits of increasing smoking cessation. *Nicotine Tob Res.* 2019;21:41-47.
33. Lee PN, Djurdjevic S, Weitkunat R, Baker G. Estimating the population health impact of introducing a reduced-risk tobacco product into Japan. The effect of differing assumptions, and some comparisons with the U.S. *Regul Toxicol Pharmacol.* 2018;100:92-104.
34. US Food and Drug Administration. Philip Morris Products S.A. Modified Risk Tobacco Product (MRTP) Applications. https://www.fda.gov/tobacco-products/advertising-and-promotion/philip-morris-products-sa-modified-

risk-tobacco-product-mrtp-applications#2. Published July 7, 2020. Accessed September 1, 2020.
35. Max WB, Sung H, Lightwood J, et al. Modelling the impact of a new tobacco product: review of Philip Morris International's Population Health Impact Model as applied to the IQOS heated tobacco product. *Tob Control.* 2018;27:S82-S86.
36. Lüdicke F, Ansari SM, Lama N, et al. Effects of switching to a heat-not-burn tobacco product on biologically relevant biomarkers to assess a candidate modified risk tobacco product: a randomized trial. *Cancer Epidemiology Biomarkers Prev.* 2019;28:1934-1943.
37. Cummings KM, Nahhas GJ, Sweanor DT. What is accounting for the rapid decline in cigarette sales in Japan? *Int J Environ Res Public Health.* 2020;17:3570.
38. Seidenberg AB, Popova L, Ashley DL, et al. Inferences beyond a claim: a typology of potential halo effects related to modified risk tobacco product claims. *Tob Control.* 2020 Oct 12;tobaccocontrol-2019-055560. doi:10.1136/tobaccocontrol-2019-055560 [Online ahead of print]
39. Stoklosa M, Cahn Z, Liber A, et al. Effect of IQOS introduction on cigarette sales: evidence of decline and replacement. *Tob Control.* 2020;29:381-387.