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Article

Modelling the population health impacts of heated tobacco products in Japan

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Abstract: Few data are available on the health impact of tobacco heating products (THPs) at the population level. We used systems dynamics modelling to estimate effects in the established THP market in Japan. We projected effects of THP use in overall mortality up to 2100 and compare those projections against a baseline scenario based on smoking rates pre-THP launch, i.e., smoking only. The model was informed using data from publicly available sources and the literature, including population size, yearly deaths and smoking prevalence with initialisation year (2004) and, births and migration from 2004 to 2065. Transitions between products were estimated from cross-sectional population surveys in Japan. Potential life-years saved with the introduction of THPs was 13 million by 2100 compared with smoking only. In worst-case scenario, population health gains would be seen with THPs risk 10–50% lower risk than smoking. Assuming equal risk for dual use and smoking, THP risk would need to be at least 10% lower than smoking to achieve a population health benefit by 2100. In credible scenarios, substantial population health gains will follow the introduction of THPs in Japan in a relatively short time frame.

Keywords: Tobacco harm reduction; tobacco heating products; THP; HTP; population health; system dynamics model, Japan projections, nicotine.

1. Introduction

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 and/or ability to quit [3]. In a tobacco harm reduction framework, tobacco health gains come from remaining smokers transitioning to an alternative lower risk product [4]. Around the world, various products, such as tobacco heated products (THPs), 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.

THPs 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 flavour compounds in an aerosol [5]. Without combustion, therefore, the formation of many of the toxicants generated in cigarette smoke is prevented or substantially reduced [6], translating to substantially reduced exposure of users to toxicants [7, 8]. A meta-analysis reviewing evidence on THP emissions of harmful and potentially harmful constituents documented reductions of 42–96% [9]. The US Food and Drug Administration (FDA) has concluded that THPs emissions reduce exposure of users to toxicants compared to smoking, and 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].

As well as chemical characteristics, behavioural elements are important determinants of whether a product might lead to harm or benefit at the population level. Some critical aspects to consider are negative behaviours that could lead to population harm, such as the initiation of THP use by never smokers who would not have otherwise used tobacco. Even more important, is the potential for people who starting use THPs to transition to smoking cigarettes, known as the gateway effect. Additionally, any benefits might be diminished by dual use – smokers adopting THP use while continuing to smoke cigarettes – rather than switching completely to THP use, or even some have raised the concern that dual use could result in greater risk than smoking alone [11].

Smoking behaviours are highly impacted by cultural [12] and regulatory aspects. In Japan smoking prevalence is nearly 18%, remaining high compared with many other countries, and among men is nearly 30% [13]. However, Japanese consumers are open to adopting new technologies. THPs were introduced to the Japanese market in 2014 and surveys have shown that 12.3% of men and 3.9% of women were using THPs in 2019 [14]. Thus, this category is now well established, which allows estimation of prevalence and transitions between smoking and THP use.

Epidemiological studies might not reveal the population effects of THPs on morbidity and mortality for many decades. In the interim, computational modelling has proved to be a useful tool to evaluate long-term population effects involving tobacco products [15]. The use of such approaches has been endorsed by the FDA [16] in their Modified Risk Tobacco Product Applications draft guidance. Some examples contributing to applications are assessing the population effects of banning menthol cigarettes [17] or assessing launching new products [18].

In this research paper, we applied a System Dynamics modelling approach to assess the population health impact of launching THPs in Japan. To inform the model we used publicly available data and transitions between products were estimated from data collected from two large cross-sectional surveys of smoking history and tobacco use in the previous 12 months [19; 20]. We present several scenarios in which we assess the nominal risk of THPs relative to smoking, including through initiation of THPs by never smokers, potential reduction in cessation due to dual use and potential additional risk from dual use.

2. Experimental Section

2.1. Model Structure

We updated a previously published system dynamics model [21] to investigate the population health effects of the introduction of THPs 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 THP user (see supplementary information). 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). Never users were defined as having used less than 100 consumables (cigarettes or THP sticks) in their lifetime; current users has 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.

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, 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 at 2004 and projections were run forward to 2100. For THP scenarios, product introduction was at year 2015. The model was developed in Vensim DSS (a Ventana Systems product) and runs under version 8.1.

2.2. Assumptions

Where possible, data available in the public domain or obtained via two cross-sectional surveys [22; 20] were used as inputs in the model. In the absence of data, certain assumptions were made to populate required inputs. First, the proportions of the population who initiated THP or dual use in the previous 12 months who would have otherwise started smoking if THPs 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 THP or dual use if THPs were not available was assumed to be 0.1%. Third, the relative fraction of THP risk to smoker risk was assumed to be 10%, based on a UK Parliament report [23]. The data behind key input parameters are provided in the supplementary information (pp 5–25).

Table 1. Key input parameters for THP scenarios

Input parameter	THP scenario A	THP scenario B	THP scenario C
Date THP introduced to marketplace	2015	2015	2015
Proportion of NC who would have started smoking without THP initiation	0.5	0.5	0.5
Proportion of CC who would have started smoking without THP initiation	0.8	0.8	0.8
Proportion of smokers who would have quit without exclusive or dual THP use	0.1	0.1	0.1
Risk ratio of THP compared to smoking excess risk	0.1	0.05 to 0.5	0.05 to 0.5
Combined relative risk to current or past use of both cigarettes and THP products	Maximum	Maximum	Additive
THP transition probabilities[1]	Weighted means	Weighted means	Weighted means

[1]Based on data in Abrahams et al. 2020 and Jones et al. 2020. Abbreviations: THP, tobacco heating product. NC, never smoker, current THP user. CC, current smoker, current THP user.

2.3. 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 THP launch in 2015. Three THP scenarios were assessed based on different combinations of assumptions for product use and relative risk level of THP compared to smoking (Table 1).

2.4. 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 [24] (see supplementary information p 19). 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 [25]. If there was a relapse to smoking or dual use, we conservatively assumed that any benefit obtained from exclusive THP use. In scenarios that involved relative risks from two products, either the maximum relative risk of the two product use statuses was used [scenarios A and B] or, the two excess risks were summed to provide an additive value [scenario C].

Product-specific mortality was estimated in the model using Garfinkel's method [26]. The modelled mortality rates in a given THP 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, Labour and Welfare [27].

2.5. 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. Transitions 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 three model assumptions. In the absence of data to inform the sensitivity limits set for the proportion of THP 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 THP 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].

3. Results

3.1. Population

Combined surveys carried out in Japan from 2018 to 2019 yielded data from 9,770 respondents [22, 20]. These surveys enabled calculation of transitions rates between smoking and THP use except for direct switching from cigarette only use to THP only use and vice versa. All estimates for transitions can be found in the supplementary information (pp 20–25).

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, Labour 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).

Table 2. Smoking quitting probabilities in Japan

Age group (years)	Male	Female
20–29	2.2%	5.4%
30–39	3.6%	3.0%

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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%

3.2. Scenario A

In Scenario A, the risk ratio of THP compared to smoking excess risk was 1.0 and the combined relative risk to current or past use of both cigarettes and THP 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).

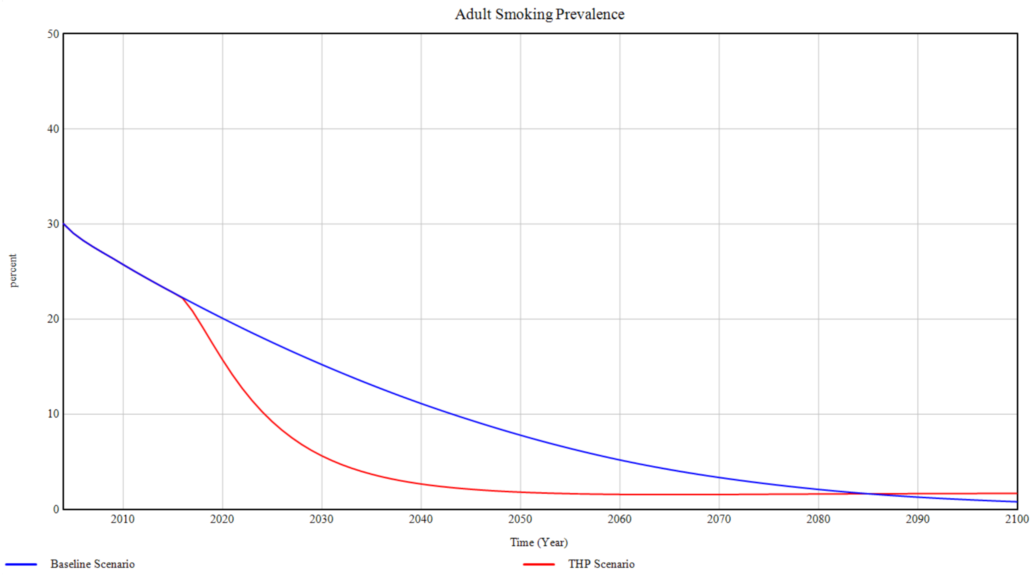
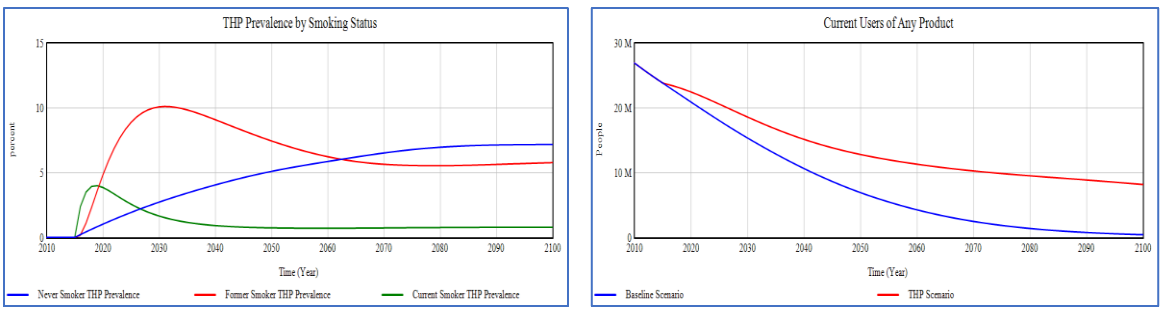


Figure 1. Adult smoking prevalence at baseline scenario versus scenario in which THP has been introduced in the Japanese market.

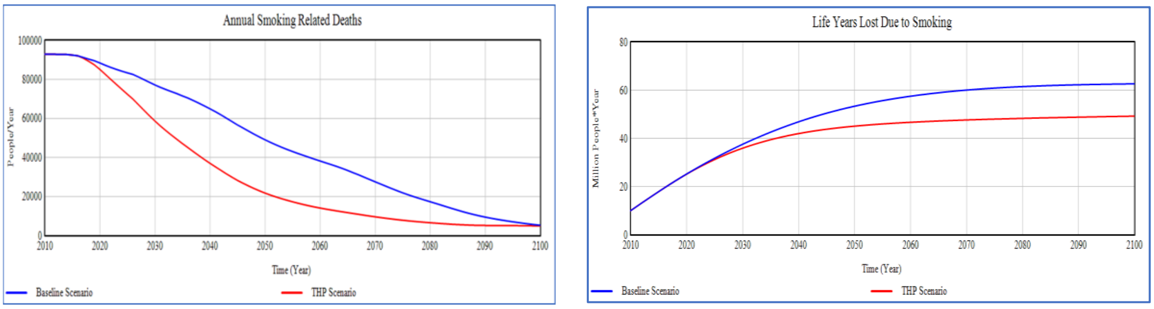
Reduction in the number of smokers in Scenario A was coupled with an increase in THP use, reaching a maximum of about 15% around 2030 across smoking history cohorts (Figure 2). The scenario also suggests that after an initial rise, dual use would decrease in favour of exclusive THP use, while uptake by never smokers would surpass that in former smokers at around 2060. In scenario A, the model also indicates that the introduction of THPs 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 THPs exclusively (Figure 2).



(**a**) (**b**)

Figure 2. (a) Composition of THP users across time; (b) nicotine use projections for baseline vs THP introduction scenarios.

Smoking-related deaths converged to very 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 gains in life-years lost due to smoking from around 2025, resulting in roughly 13 million life-years saved by 2100 (Figure 3).



(**a**) (**b**)

Figure 3. (**a**) Annual smoking related deaths; (**b**) life-years lost due to smoking.

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 (Figure 4).

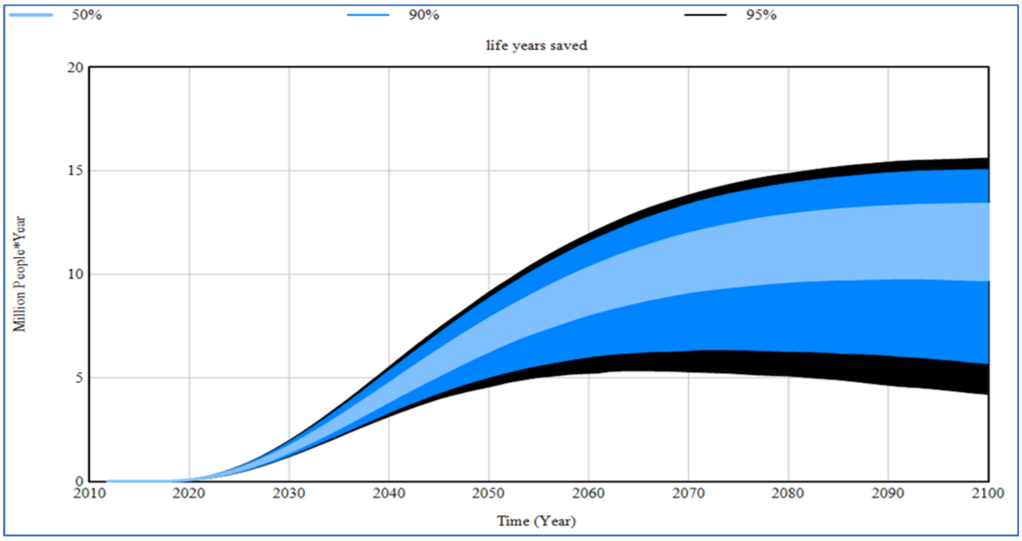


Figure 4. Projection of life-years saved with uncertainty boundaries produced using confidence intervals from our population study.

3.3. Scenario B

In scenario B, we assessed the importance of the relative risk of using THP with respect to smoking. The model projected gain in life-years saved by 2100 for all credible risk levels (Figure 5), and a break-even level by 2100 with a risk ratio greater than 90% (see supplementary information p

26). After 2100, harm from THPs would start to be predominant as smoking would have largely phased out 30–40 years earlier.

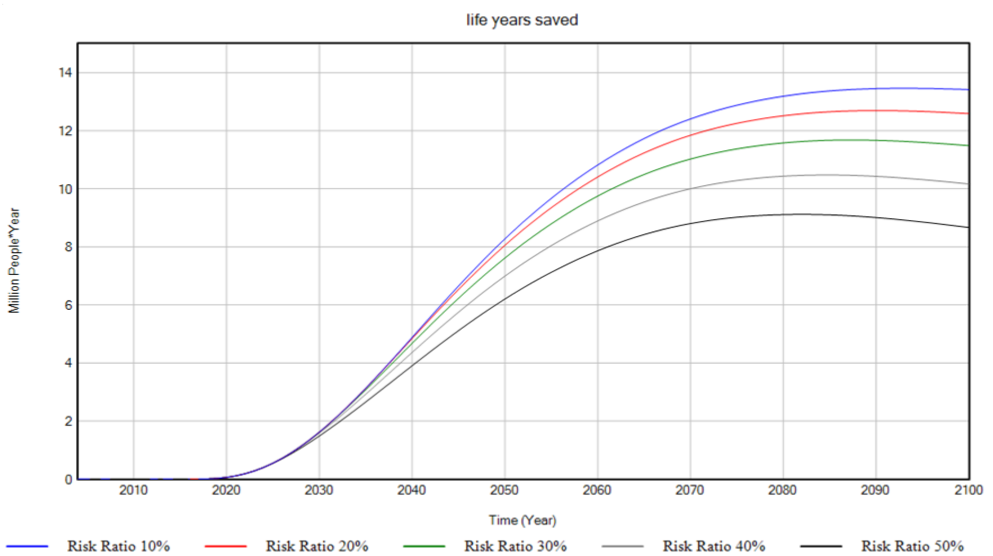


Figure 5. Projections of life-years saved with different risk ratios for smoking and THP use.

3.4. Scenario C

In a the worse-case scenario, scenario C used additive risk to assess the health effects of dual use of THPs and cigarettes in which the relative risk were additive, (relative risk of smoking plus a risk ratio of 0.1 for THP 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 THP risk ratio of 0.1 would have a relative risk of 1.649.

In an additive risk scenario, while with a risk ratio for THP use below approximately 20%, the model suggested gains in life-years saved for the whole run time to 2100 (Figure 6). 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 exclusive THP use. Later, however, as transition from dual to exclusive used increased, the model suggested overall population gains in by 2100. Beyond 2100, THP 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 (see supplementary information p 26).

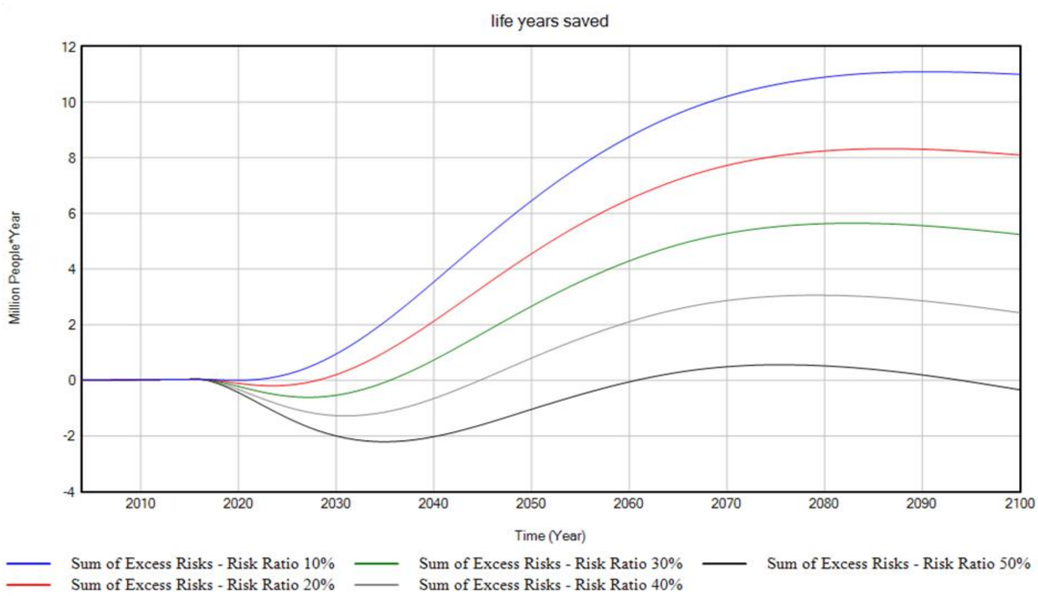


Figure 6. Projection of life-years saved in the additive risk scenario with risk ratios of 10–50%.

4. Discussion

THPs were first commercialised in Japan in 2014 and are now well established products, by 2019, with 12.3% of men and 3.9% of women using them [14]. In addition, the fact that e-cigarettes with nicotine are banned in Japan has created a unique ecosystem to study the potential role of THPs in a smoking harm reduction framework. Our systems dynamics modelling for Japan showed reduced mortality projections, leading to about 13 million life-years saved with the introduction of THPs by 2100.

This model was populated using publicly available data and transitions between smoking and THP use were calculated based on a survey of 9,770 participants. Our probability calculations for smoking initiation were in line with previous reports [28, 29]. Our quitting probabilities are more conservative than those reported by Tabuchi and colleagues 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 [30].

Jones et al [20] population study points to low initiation of THP use among never smokers at 0.3%. Of these only one (3%) transitioned from THP into dual use and none reported transitioning to smoking alone. These low values should mitigate concerns about potential gateway effects.

While there is substantial literature concerning the potential effects of e-cigarettes on population health [31, 32], few data are available on the population effects of THPs. Older-generation THPs were not successful in the USA [9] and newer generations might have been too recently introduced in that country to have attracted sufficient interest from tobacco modelling 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 THP 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 USA [34]. However, the validity of the projections has been questioned, mainly because transition rates to and from THPs in the US were speculative as the product was not commercially available in that country [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 two different conditions: considering the risk to be the maximum of the product exposure risk or to be additive. Following best 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 been found not to being 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 and colleagues [37] also seem to support this phenomenon is happening in Japan. They found that since the introduction of THPs, cigarette sales have fallen significantly faster than projected, but that the combined sales of cigarettes and THP sticks has continued on the original tobacco consumption trajectory.

Our third assumption related to the proportion of THP users who would have quit all tobacco products instead of switching to THPs. We assumed that a maximum of 10% of those switching to THP would have quit if THPs were not available as a conservative assumption supported by literature citing quitting rates among men to be 3.7% to 10.7% for men and from 9.9% to 16.3% for women [30].

A limitation of the study was that all definitions were based on 1-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. Such transitions were therefore captured by transitions to dual use and then to exclusive use.

5. Conclusions

In conclusion, our model suggests that tipping points for the potential harm from introducing THP products in Japan would be so far in the future that future generations are not likely to be using even the same categories of products assessed here, making future certainty low. However, present certainty of the effects is high, evidence in THP use risk suggests them to be lower risks than cigarettes [23] and the harm caused by smoking is undeniable. Our model suggests that based on the current smoking behaviours observed in Japan, the introduction of THPs will start returning health gains in a relatively short term in the most credible scenarios, led by smokers completing switching to THP products.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, S1 Data Sources, including: Table S1: Public data sources; Figure S1. Representation of transitions (arrows) in a 2-product model and cohorts or stocks; Table S2. Description of model stock definitions; Table S3. Population estimates for Japan in year 2004; Table S4. Japan historic birth rate; Table S5. Japan projected birth rate; Table S6. Initial mortality rates; Table S7. Projected annual reduction in death rates; Table S8. Life expectancy in Japan; Table S9. Historical net migration in Japan. (Top) Male, (Bottom) Female; Table S10: Projected net migration in Japan. (Top) Male, (Bottom) Female; Table S11. Prevalence by smoking status; Table S12. Former smoker quit distribution by sex; Table S13. Ever smoking initiation; Table S14. Annual decline in smoking initiation; Table S15. Annual quitting probability; Table S16. Annual smoking relapse probability; Table S17. Mortality relative risk for current smokers; Table S18. Decay in all mortality risk for former smokers; Table S19. Assumption of risk ratio of THP use to smoking; Table S20. Transition rates between into and between the 2 products. S2 Supplementary Outputs, including: Figure S2. Projection of Life Years Saved for additive risk scenario with risk ratios between 10 -50% including 90% risk ratio; Figure S3. Life-yeas saved with 40% risk ratio in an additive scenario.

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