Regulatory Toxicology and Pharmacology 100 (2018) 92–104

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

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.

Peter N. Lee[a], Smilja Djurdjevic[b,*], Rolf Weitkunat[b], Gizelle Baker[b]

[a] P.N. Lee Statistics and Computing Ltd., 17 Cedar Road, Sutton, Surrey, SM2 5DA, United Kingdom
[b] PMI R&D, Philip Morris Products S.A., Quai Jeanrenaud 5, CH-2000, Neuchâtel, Switzerland

ARTICLE INFO

Keywords:
Smoking
Modelling
Attributable risk
Reduced-risk tobacco product
Harm reduction

ABSTRACT

We estimated, using previously described methodology, the population health impact of introducing a reduced-risk tobacco product (RRP) into Japan. Various simulations were carried out to understand the impact on the population in different situations over a 20-year period from 1990. The overall reduction in tobacco-attributable deaths from lung cancer (LC), ischemic heart disease (IHD), stroke, and chronic obstructive pulmonary disease (COPD) for men and women combined was estimated to be 269,916 over the period if tobacco use disappeared completely at baseline. In contrast, reductions ranging from 167,041 to 232,519 deaths were estimated if the RRP totally replaced smoking at baseline (assuming that switching to it had an effect equivalent to 70%–90% of the effect of quitting). If, more plausibly, the RRP were introduced at baseline, with uptake rates consistent with the known uptake of the RRP *IQOS*®, the reductions would still be substantial (from 65,126 to 86,885 deaths). Expressed as a percentage of attributable deaths, these proportions are larger than those for the U.S., based on likely uptake rates. We discuss various limitations of the approach, though none should affect the conclusion that the introduction of an RRP into Japan will substantially reduce tobacco-related deaths.

1. Introduction

Our main objective is to compare the estimated population health impact of introducing an RRP into Japan under alternative assumptions about its rate of uptake. We also compare our estimates with those derived in various situations where the RRP is not introduced, including reductions in prevalence of conventional cigarette (CC) smoking according to World Health Organization (WHO) Targets and Projections, and an extreme situation in which there is no further use of tobacco. We also present, for comparative purposes, a similar set of estimates for the U.S.

The estimates for Japan are particularly relevant, as Philip Morris' heat-not-burn product, the Tobacco Heating System, sold under the brand name *IQOS*, was introduced there in 2015 with a level of uptake suggesting that within 10 years of its introduction, 47% of tobacco users will use the RRP exclusively, and 8% will be dual users of CCs and the RRP. (Note that hereafter in this paper, for simplicity, those who use CCs exclusively are referred to as CC smokers, and those who use RRPs exclusively are referred to as RRP users.)

The method we use to access the population health impact of introducing an RRP into a country is as earlier described (Weitkunat et al., 2015) and involves two components.

The first is the Prevalence (P-) component, a Markov chain state-transition model that starts in a specified year with a group of individuals of a given sex and age range who have a distribution of CC smoking habits representative of the national population at that time. This group is then followed over discrete time intervals for a defined length of time, under both a "Null Scenario" and an "Alternative Scenario," using different sets of tobacco use transition probabilities (TTP). In the Null Scenario, RRPs are never introduced, and the TTPs are appropriate for CC use, with the cigarette smoking status of an individual (never, current, former) updated at each interval. In the Alternative Scenario, RRPs are introduced at the start of follow up, and the TTPs allow for switching between five groups (never tobacco,

Abbreviations: CC, conventional cigarette; COPD, chronic obstructive pulmonary disease; E-component, epidemiologic component; H, half-life; IHD, ischaemic heart disease; LC, lung cancer; NEM, negative exponential model; P-component, prevalence component; RR, relative risk; RRP, Reduced Risk Tobacco Product; TTP, tobacco use transition probability; WHO, World Health Organization; YLL, years of life lost; YLS, years of life saved

* Corresponding author.
E-mail address: Smilja.Djurdjevic@pmi.com (S. Djurdjevic).

https://doi.org/10.1016/j.yrtph.2018.10.010
Received 29 August 2018; Received in revised form 15 October 2018; Accepted 20 October 2018
Available online 24 October 2018

current CC smoking, current RRP use, current dual use, former tobacco). After completion of the P-component, each individual then has a complete tobacco product use history over the follow-up period under each Scenario. Note that the modelling described here ignores tobacco products other than CCs and RRPs.

The Epidemiologic (E-) component then uses the tobacco histories to estimate, for each individual, the relative risks (RR) of LC, IHD, stroke, and COPD compared with that of never tobacco users at each year of follow-up and for each Scenario. The estimation involves an extension of the negative exponential model (NEM), described in detail elsewhere (Lee et al., 2017), which allows for multiple changes in tobacco habits. Apart from the tobacco histories, the NEM also requires estimates of the effective dose for current RRP use and for dual use, compared to that for current CC smoking (which is taken as one unit), as well as estimates of the RR for continued smoking and of the quitting half-life (H) for each disease, with H being the time after quitting when the excess RR (RR − 1) reaches half of that for continuing smokers. Note that although the estimation of the RR for an individual uses the full smoking history, it does not specifically take into account the amount smoked. However, the effective dose for dual users may be set to reflect a reduced consumption of CCs compared with CC smokers.

Separately for each Scenario, the average RRs for each disease for individuals of a given sex and age group are then calculated for each follow-up year, from which proportions of tobacco-attributed deaths can be derived. These are then converted to numbers using national mortality estimates by sex, age group, and year. Differences between Scenarios in the estimated numbers and proportions then quantify the effect of RRP introduction.

In addition to estimating effects on numbers of deaths and death rates, one can also compare years of life lost (YLL) in the Alternative Scenario compared with the Null Scenario using the method of Gardner and Sanborn (1990). YLL(N) is calculated by summing the product of the number of deaths occurring in each age group by the number of years of life remaining up to a given age of N years, with N taken as 75 years in our estimates. For the 40–44 years age group, for example, where the mean age is taken to be 42.5 years, the number years of life remaining is then taken to be 75–42.5 = 32.5 years. For age groups above 70–74 years, the number of years remaining is taken to be zero. We refer to reductions in YLL in the Alternative Scenario compared with the Null Scenario as years of life saved (YLS).

As noted elsewhere (Weitkunat et al., 2015), these estimates of the effect of RRP introduction can, if required, be corrected for survival differences between Scenarios. The methodology can also be used to compare the Null Scenario with Alternative Scenarios, in which RRPs are not introduced but different sets of TTPs for CC smoking are used.

In the applications of the model described here, we use a "hindcasting" approach, in which a population of individuals is followed from 1990 to 2010 in each simulation. The Null Scenario re-predicts a past that has already occurred, while the Alternative Scenarios produce counter-factual predictions, which vary depending on the assumptions made. The advantages of this approach, as compared with an approach in which the future is predicted, are that there is a real world for calibrating the model under the Null Scenario and that the effect of exogenous factors on mortality rates are already taken into account.

When applying the model, we start with a population aged 10–79 years, with individuals dropping out of the calculations when they reach age 80 years. This is partly because cause-of-death certification is unreliable at higher ages and partly because our estimates of the population health impact also include YLL, which are not affected by deaths above age 74.

While the Alternative Scenarios considered, described in detail in the Methods section, mainly concern different assumed uptake rates of the RRP, we also ran separate simulations in which the effective dose (F) for the RRP was taken as either 0.1, 0.2, or 0.3, with that for dual use correspondingly set as (1 + F)/2. The variation in F is consistent with the uncertainty based on biomarkers and clinical findings for *IQOS* (Martin et al., 2018).

2. Methods

2.1. Common features of each simulation

Each simulation involved the follow up of 100,000 individuals, initially aged 10–79 years, in one-year intervals from 1990, with the tobacco use status of each member of the simulated population estimated at each year of follow up until the year 2010 (or age 79, if that came earlier). For each of the situations described in section 2.4, separate simulations were conducted for each sex.

2.2. Population at baseline

As previously described (Lee et al., 2017), each individual in a simulation is randomly allocated at baseline to a year of age, then to a CC smoking group (never, current, or former), and then (if a former smoker) to an age of quitting. The age distributions used for 1990 are as published by the United Nations (United Nations Department of Economic and Social Affairs, 2013). The distributions of smoking for 1990 are based on data from International Smoking Statistics (Forey et al., 2002; Forey and Lee, 2002; Lee et al., 2009). The distribution of time quit for former smokers for Japan comes from the Japanese Cessation Study, an online survey conducted by Interwired in 2009 (http://www.dims.ne.jp/timelyresearch/2010/100112/), while that for the U.S. comes from the National Health Interview Survey data for 2006 (www.calc.gov/nchs/nhis.htm).

Table 1 (males) and Table 2 (females) present the age-specific distributions of population and smoking habits for each country used to assign the initial status of each member of the simulated population.

2.3. Estimation of histories of tobacco use for the Null Scenario

For Japan, the TTPs for the Null Scenario were derived as described in Supplementary File 1. For the U.S., the Null Scenario TTPs were as presented previously, where they were shown to predict prevalences of current and former smoking for 1995, 2000, and 2005 that were adequately close to those reported in International Smoking Statistics (Lee et al., 2017). While there was little evidence that TTPs for the U.S. varied by sex and period of follow up, this was not so for Japan, and the TTPs used differed by sex and by period (1990–1999, 2000–2009).

The TTPs for the Null Scenario are shown for both countries in Table 3.

Prevalences for 1995, 2000, and 2005 were compared with those reported in International Smoking Statistics to test the validity of the TTPs.

2.4. Estimation of histories of tobacco use for the Alternative Scenarios

For the Alternative Scenarios, the TTPs varied according to the situation. For Japan, seven situations were tested.

1. **No further use of tobacco.** All current CC smokers at baseline immediately stop smoking with no further initiation or re-initiation of tobacco use.
2. **CC smoking totally replaced by RRP use.** All current CC smokers in 1990 immediately switch to the RRP. Subsequent initiation, re-initiation, and quitting rates are as in the Null Scenario but only involve switches to or from the RRP.
3. **Main.** This uses TTPs designed so that in 2000, about 47% of tobacco users are RRP users, 8% are dual users, and the remainder are CC smokers. To ensure comparability with the TTPs for the Null Scenario, various constraints were applied: the sum of the three TTPs for initiation (as CC, RRP, or dual use) in the RRP Scenario equaled the TTP for initiation in the Null Scenario; the sum of the

Table 1
Age-specific data on population and smoking habits for 1990 – males.[a]

Country	Age	Population (hundreds)	% current smokers	% former smokers	Distribution of time of quit (years)[b]					
					0	1–2	3–5	6–10	11–20	21 +
Japan	10–14	43555	0.0	0.0	–	–	–	–	–	–
	15–19	51159	28.7	0.0	–	–	–	–	–	–
	20–24	44177	62.6	3.8	25.9	48.1	22.2	3.7	–	–
	25–29	40407	66.5	6.8	25.9	48.1	22.2	3.7	19.8	–
	30–34	38933	67.7	10.3	16.5	15.5	28.0	19.7	19.8	0.6
	35–39	45296	65.6	12.7	16.5	15.5	28.0	19.7	30.2	0.6
	40–44	52955	60.3	14.4	9.0	9.0	22.4	13.0	30.2	16.4
	45–49	44388	58.5	16.1	9.0	9.0	22.4	13.0	20.5	16.4
	50–54	39633	57.1	17.8	7.3	8.9	14.7	14.8	20.5	33.8
	55–59	37399	53.8	20.7	7.3	8.9	14.7	14.8	19.5	33.8
	60–64	31883	56.5	24.6	4.6	5.0	13.4	11.6	19.5	46.0
	65–69	21418	51.1	27.2	4.6	5.0	13.4	11.6	19.5	46.0
	70–74	15255	44.6	27.6	4.6	5.0	13.4	11.6	19.5	46.0
	75–79	11779	39.0	29.1	4.6	5.0	13.4	11.6	19.5	46.0
U.S.	10–14	90334	0.0	0.0	–	–	–	–	–	–
	15–19	90246	20.0	4.4	69.4	30.6	–	–	–	–
	20–24	101190	30.7	9.1	30.2	40.3	29.5	–	–	–
	25–29	109227	35.1	14.4	27.3	30.2	21.1	21.4	–	–
	30–34	112247	34.7	19.7	20.3	15.4	36.7	23.7	3.9	–
	35–39	101430	33.0	24.8	10.2	11.3	18.5	29.6	30.4	–
	40–44	87915	31.9	30.5	8.8	5.1	13.5	15.9	56.7	–
	45–49	67089	32.0	36.6	7.2	6.3	10.6	17.5	35.8	22.6
	50–54	57684	30.1	42.2	8.6	6.8	11.0	8.7	33.4	31.5
	55–59	50687	28.5	46.9	7.7	6.5	12.9	17.4	22.2	33.3
	60–64	50198	25.8	51.5	2.5	3.6	7.7	13.0	30.9	42.3
	65–69	45723	21.6	56.1	1.8	4.6	8.7	12.9	28.3	43.7
	70–74	35251	18.6	60.6	0.6	1.5	14.8	8.7	27.2	47.2
	75–79	25372	15.2	55.7	1.8	4.9	2.8	6.3	29.7	54.5

[a] Sources used: Population – United Nations Department of Economic and Social Affairs Population Division (2015); Prevalence of current and former smoking – (Forey et al., 2002; Forey and Lee, 2002; Lee et al., 2009); Time of quitting for Japan – (http://www.dims.ne.jp/timelyresearch/2010/100112/); Time of quitting for U.S. – www.cdc.gov/nchs/nhis.htm.

[b] The full data sets separate 1–2 years into 1 and 2 years, 11–20 years into 11–15 and 16–20 years, and 21 + years into 21–30, 31–40, and 41–50 years.

three TTPs for re-initiation in the RRP Scenario equaled the TTP for re-initiation in the Null Scenario; and the three TTPs for quitting in the RRP Scenario each equaled the TTP for quitting in the Null Scenario.

4. **WHO Target.** This uses TTPs designed to reduce CC smoking prevalence by about 30% within 15 years (i.e., between 1990 and 2005). This is analogous to the WHO's stated target (World Health Organization, 2015) to achieve a 30% reduction in smoking prevalence between 2010 and 2025.
5. **WHO Projection.** This uses TTPs designed to reduce CC smoking prevalence by about 14% between 1990 and 2005. This is analogous to the WHO's projection (World Health Organization, 2015) of a 14% reduction between 2010 and 2025.
6. **WHO Target with Main.** This uses TTPs designed to reduce the prevalence of tobacco use by about 30% between 1990 and 2005 and to have the distribution of RRP use in 2000 described for Situation 3. The constraints applied were as for Situation 3, except that the cessation rate from CC use was increased from that in the Null Scenario.
7. **WHO Projection with Main.** As Situation 6, but the prevalence of tobacco use is only reduced by about 14% between 1990 and 2005.

RRPs are not introduced in Situations 1, 4, and 5. For the other four situations, the three different sets of effective doses described above were used, so that in all there were 15 simulations for each sex for Japan.

For the U.S., eight situations were tested. Situations 1 and 2 correspond to those for Japan. For the Main situation, 3, the TTPs used for the U.S. were different, designed so that in 2000, about 15% of tobacco users are RRP users, 2% are dual users, and the remainder are CC smokers. This represented a recent view of the likely extent of uptake of *IQOS* in the U.S. if it were to be licensed for use.

Situations 4 to 7 for the U.S. correspond to those for Japan, combining the country-specific estimates of RRP uptake with the TTPs designed to meet the WHO Target and WHO Projection criteria.

One additional Alternative Scenario, 8, was tested for the U.S., based on an **extreme dual use increase** assumption. This uses TTPs designed so that in 2000, about 5% of tobacco users are RRP users, 12.5% are dual users, and the remainder are CC smokers. The prevalence of RRP use in 2000 is similar to that for the U.S. Main situation, but the proportion of dual users among RRP users is much higher (about 70% vs. about 10%). Such an extreme increase in dual use for the higher expected prevalence of RRP use in Japan has not been considered, as post-market data for *IQOS* suggests that this is unlikely (Langer et al., 2018).

The additional situation for the U.S. brings the total number of simulations for each sex up to 18.

The full set of Alternative Scenario TTPs for all the situations is presented in Supplementary File 2.

2.5. Factors affecting TTPs

It should be noted that for both the Null and the Alternative Scenarios, the TTPs may be modified under certain conditions. Thus, quitting rates are multiplied by two for an individual who has previously quit or has quit for less than two years. Also, the rate of switching from current RRP only to current CC only was set as zero if the individual had used the RRP for more than one year. These modifications are not relevant in all situations.

Table 2
Age-specific data on population and smoking habits for 1990 - females.[a]

Country	Age	Population (hundreds)	% current smokers	% former smokers	Distribution of time of quit (years)[b]					
					0	1–2	3–5	6–10	11–20	21 +
Japan	10–14	41428	0.0	0.0	–	–	–	–	–	–
	15–19	48794	10.8	0.0	–	–	–	–	–	–
	20–24	42846	14.3	2.3	18.1	29.1	36.0	13.2	3.6	–
	25–29	39567	13.9	2.2	18.1	29.1	36.0	13.2	3.6	–
	30–34	38328	13.9	2.4	14.4	17.2	24.8	18.3	24.9	0.3
	35–39	44859	13.0	2.1	14.4	17.2	24.8	18.3	24.9	0.3
	40–44	52594	11.7	1.7	9.4	10.0	23.7	12.5	30.5	13.8
	45–49	44952	10.7	1.4	9.4	10.0	23.7	12.5	30.5	13.8
	50–54	40605	10.1	1.5	8.8	10.3	19.1	4.4	22.0	35.3
	55–59	39016	8.7	1.7	8.8	10.3	19.1	4.4	22.0	35.3
	60–64	34744	10.6	2.0	7.1	0.0	28.6	14.3	21.4	28.6
	65–69	28795	8.6	2.2	7.1	0.0	28.6	14.3	21.4	28.6
	70–74	22128	8.9	2.6	7.1	0.0	28.6	14.3	21.4	28.6
	75–79	17972	6.8	2.9	7.1	0.0	28.6	14.3	21.4	28.6
U.S.	10–14	85026	0.0	0.0	–	–	–	–	–	–
	15–19	87465	18.5	5.0	60.2	39.8	–	–	–	–
	20–24	94945	26.9	12.8	34.1	34.0	31.9	–	–	–
	25–29	106184	29.2	15.9	17.3	19.9	31.1	31.7	–	–
	30–34	110821	29.5	18.8	20.1	22.8	19.7	26.7	10.7	–
	35–39	101770	26.6	21.5	10.0	12.6	20.3	24.2	32.9	–
	40–44	91022	26.4	22.1	10.7	16.7	19.9	20.6	32.1	–
	45–49	71029	26.7	23.2	9.1	7.8	11.1	20.2	32.9	19.0
	50–54	59240	25.5	24.8	5.6	9.8	9.9	20.9	26.2	27.6
	55–59	55061	22.4	26.7	4.5	5.6	8.4	11.2	28.9	41.4
	60–64	57273	20.4	28.5	2.7	5.0	9.1	11.6	33.2	38.4
	65–69	55804	15.8	30.3	4.1	3.2	7.9	12.8	22.5	49.5
	70–74	46360	14.1	32.1	0.5	3.4	2.6	11.8	25.8	55.9
	75–79	37422	10.0	19.6	1.2	1.9	3.1	6.3	28.3	39.4

[a] Sources used: Population – United Nations Department of Economic and Social Affairs Population Division (2015); Prevalence of current and former smoking – (Forey et al., 2002; Forey and Lee, 2002; Lee et al., 2009); Time of quitting for Japan – (http://www.dims.ne.jp/timelyresearch/2010/100112/); Time of quitting for U.S. – www.cdc.gov/nchs/nhis.htm.

[b] The full data sets separate 1–2 years into 1 and 2 years, 11–20 years into 11–15 and 16–20 years, and 21 + years into 21–30, 31–40, and 41–50 years.

Table 3
Monthly tobacco transition probabilities (per million) in the Null Scenario.

Period (years)	Age	Initiation (P_{NC})			Quitting (P_{CF})			Re-initiation (P_{FC})		
		Japan males	Japan females	U.S.	Japan males	Japan females	U.S.	Japan males	Japan females	U.S.
1–10	10–14	4000	1500	2000	0	0	500	0	0	240
	15–19	11000	2000	3500	2000	4000	1500	960	1920	720
	20–24	3500	1000	2000	2000	2000	2000	960	960	960
	25–29	3500	1000	1000	2000	2000	2000	960	960	960
	30–34	0	1000	500	500	1000	2000	240	480	960
	35–54	0	0	0	500	500	2000	240	240	960
	55–64	0	0	0	5000	1000	2500	2400	480	1200
	65–69	0	0	0	5000	1000	3000	2400	480	1440
	70–74	0	0	0	5000	1000	3500	2400	480	1680
	75–79	0	0	0	5000	1000	4000	2400	480	1920
11–20	10–14	1000	250	2000	0	0	500	0	0	240
	15–19	9000	4000	3500	18000	16000	1500	8640	7680	720
	20–24	1000	1000	2000	2500	16000	2000	1200	7680	960
	25–29	1000	1000	1000	2500	16000	2000	1200	7680	960
	30–34	0	1000	500	2500	16000	2000	1200	7680	960
	35–54	0	0	0	5000	8000	2000	2400	3840	960
	55–64	0	0	0	8000	8000	2500	3840	3840	1200
	65–69	0	0	0	16000	8000	3000	7680	3840	1440
	70–74	0	0	0	16000	8000	3500	7680	3840	1680
	75–79	0	0	0	16000	8000	4000	7680	3840	1920

The first period relates to the 10 year period starting in 1990 while the second period relates to the 10 year period starting in 2000.
The probabilities of transition between the three states N = never, C = current, and F = former, are described by P followed by two subscripts, the first representing the state changed from, and the second the state changed to.
P_{CF} is multiplied by 2 if the individual has previously quit.
P_{FC} is multiplied by 2 if the individual has quit for 2 years or less.
Note that RRPs are not introduced in the Null Scenario.

Table 4
Assumed values of the relative risk for continued CC smoking (RR) and the quitting half-life (H) by disease.

	Age (years)	LC		IHD	Stroke	COPD	
		Japan	U.S.	Japan and U.S.	Japan and U.S.	Japan	U.S.
Relative risk	Any	3.59	11.68			2.86	4.56
	to 54			3.38	2.48		
	55 to 64			2.32	2.13		
	65 to 74			1.70	1.39		
	75 to 79			1.27	1.06		
Half-life	Any				4.78	13.32	13.32
	to 49	6.98	6.98	1.47			
	50 to 59	10.39	10.39	5.32			
	60 to 69	10.60	10.60	7.48			
	70 to 79	12.99	12.99	13.77			

For the U.S., the sources of the estimates are as given in the footnote to Lee et al. (2017) Table 5. The sources are the same for Japan, except that the RR for LC is as given in Lee et al. (2018).

2.6. Estimating RRs based on the tobacco use histories

For each disease, the estimates of the RR for continued CC smoking and of H were derived from meta-analyses of published data. The estimates and the sources used are given in Table 4.

The country-, sex-, and age-specific data on national population size for the years 1990–2010 were as published by the United Nations (United Nations Department of Economic and Social Affairs Population Division, 2015) for both countries.

The data on numbers of deaths from LC, IHD, stroke, and COPD were extracted from Vital Statistics Japan for Japan and from WHO for the U.S.

The data on population size and numbers of deaths for the years 1990–2010 are presented in Supplementary File 3.

The method of estimating the number of deaths and the increase in death rates associated with smoking is as described earlier (Lee et al., 2017). Unless otherwise indicated, results are presented without adjustment for any change in population size associated with the Alternative Scenario.

3. Results

Fuller details of the analyses conducted are available in Supplementary File 4 and Supplementary File 5.

Table 5 shows the prevalence of tobacco use in Japan for both Scenarios for the Main situation. Over the 20 years, the prevalence of current smoking in the Null Scenario declined sharply in males, and that of former smoking increased. The prevalence of former smoking increased in Japanese males, and that of current smoking decreased with age. The prevalence of current and former smoking was much lower in females than males, with the prevalence of former smoking increasing with time. In the Alternative Scenario, RRP users exceeded CC smokers by the year 2000, consistent with the specification of the Main situation. The prevalence of dual use did not increase after 1995.

Fig. 1 (males) and Fig. 2 (females) compare the Null Scenario smoking prevalence estimates for Japan with those given by the Japanese Ministry of Health. The correspondence between the pairs of estimates for current smoking and for former smoking appears quite reasonable. Note that the scales are different for the two sexes to allow for the higher prevalences in males. This has the effect of emphasizing

Table 5
Prevalence of tobacco use in the Main situation for Japan.

Sex	Age	Year	Null Scenario			Alternative Scenario				
			Never	Current	Former	Never	CC	RRP	Dual	Former
Male	30–34	1990	21.35	68.28	10.37	21.35	68.28	0.00	0.00	10.37
		1995	23.68	64.77	11.55	24.02	37.96	21.74	5.13	11.14
		2000	23.72	61.50	14.78	23.97	25.93	30.16	5.19	14.76
		2005	34.64	48.10	17.27	34.68	17.38	27.45	4.08	16.42
		2010	37.95	43.38	19.67	36.64	14.11	26.72	3.76	18.78
Male	50–54	1990	24.33	57.83	17.84	24.33	57.83	0.00	0.00	17.84
		1995	25.10	56.87	18.03	25.10	32.43	19.80	5.02	17.64
		2000	24.95	57.53	17.53	24.95	20.78	31.58	5.36	13.33
		2005	21.39	49.69	28.93	21.39	13.34	32.73	4.38	28.16
		2010	21.35	41.72	36.93	21.35	8.81	30.33	3.25	36.26
Male	70–74	1990	27.65	45.38	26.98	27.65	45.38	0.00	0.00	26.98
		1995	21.72	41.95	36.33	21.72	24.49	14.46	3.80	35.22
		2000	19.49	38.08	42.43	19.49	14.22	19.94	4.06	42.29
		2005	25.37	25.29	49.34	25.37	10.11	12.34	3.57	48.61
		2010	24.33	22.79	52.88	24.33	9.59	10.62	3.40	52.06
Female	30–34	1990	83.59	14.02	2.40	83.59	14.02	0.00	0.00	2.40
		1995	78.99	17.24	3.77	79.32	9.58	6.10	1.38	3.62
		2000	73.68	20.55	5.77	74.47	9.16	9.60	1.50	5.27
		2005	72.03	13.83	14.14	71.73	3.01	5.84	1.63	13.78
		2010	72.64	11.18	16.18	72.55	5.71	4.30	1.19	16.24
Female	50–54	1990	87.81	10.35	1.84	87.81	10.35	0.00	0.00	1.84
		1995	87.99	10.27	1.75	87.99	5.87	3.39	0.81	1.94
		2000	87.00	10.75	2.25	87.00	3.74	6.14	0.93	2.19
		2005	85.19	8.43	6.37	85.19	2.30	5.59	0.78	6.13
		2010	80.73	8.65	10.62	80.77	2.32	5.39	0.87	10.65
Female	70–74	1990	88.68	8.43	2.89	88.68	8.43	0.00	0.00	2.89
		1995	89.74	7.68	2.58	89.74	4.57	2.93	0.39	2.38
		2000	87.74	9.21	3.05	87.74	3.42	4.96	0.68	3.20
		2005	89.10	5.91	4.99	89.10	1.75	3.69	0.50	4.97
		2010	87.81	4.86	7.33	87.81	1.48	3.49	0.52	6.71

Note: In the Null Scenario, Current and Former refer to CC smoking.

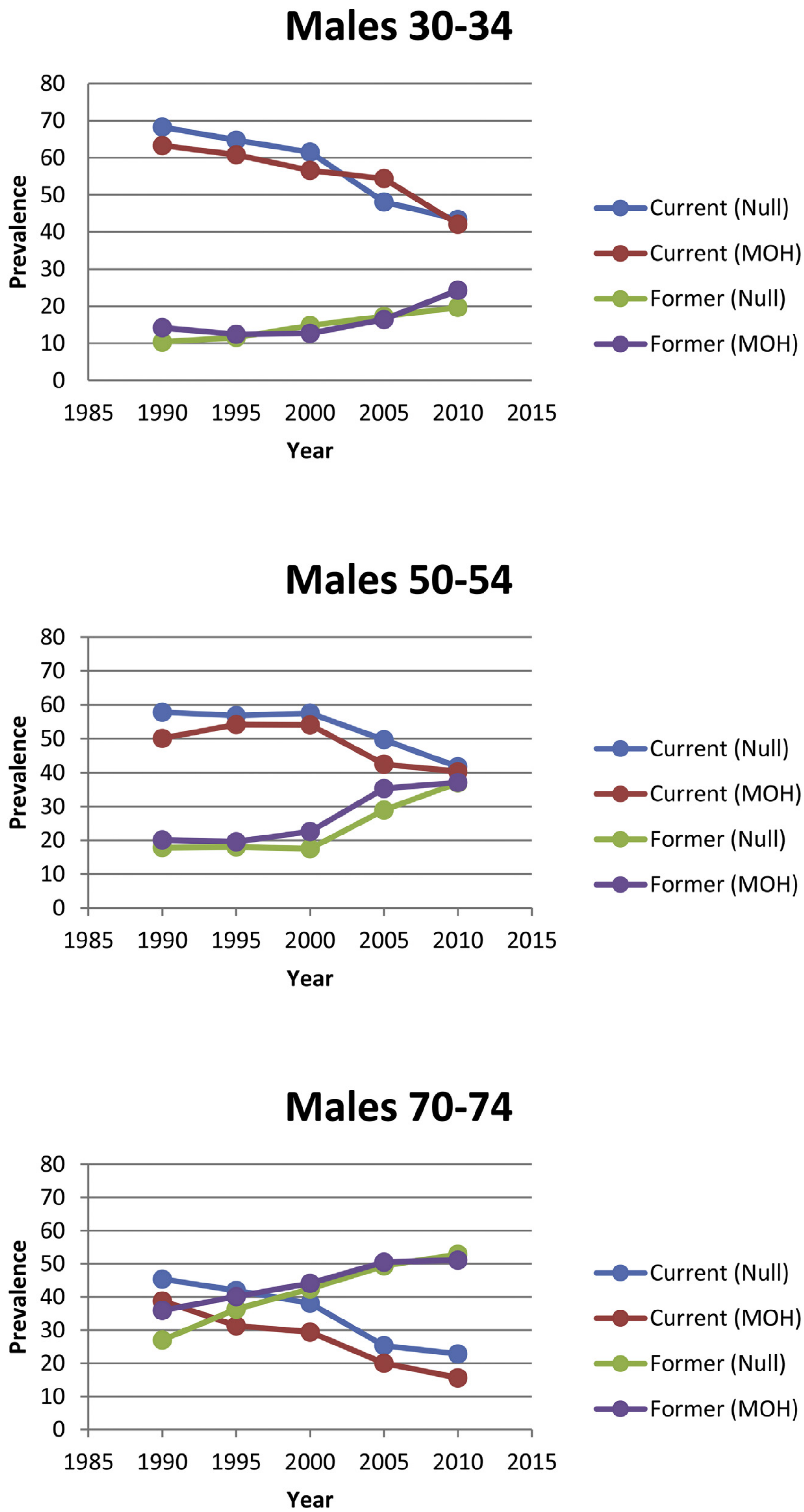

Fig. 1. Compares Null Scenario and Japan Ministry of Health estimates of current and former smoking prevalences for Japanese males at ages 30–34, 50–54, and 70–74 for the years 1990, 1995, 2000, 2005, and 2010.

small differences in females compared with males.

Table 6 shows the prevalence of tobacco use in the U.S. for both Scenarios for the Main situation. Over the 20-year period, the distribution of smoking in the U.S. in the Null Scenario changed little in 50–54 and 70–74 year-old females, but in 30–34 year-old females and males of all age groups, there was an increase in never smokers and a decrease in former smokers. The prevalence of current smoking was somewhat higher in males than females. In the Alternative Scenario, the proportion of RRP only users clearly increased with time. The proportion of dual users was always less than 1% of the population.

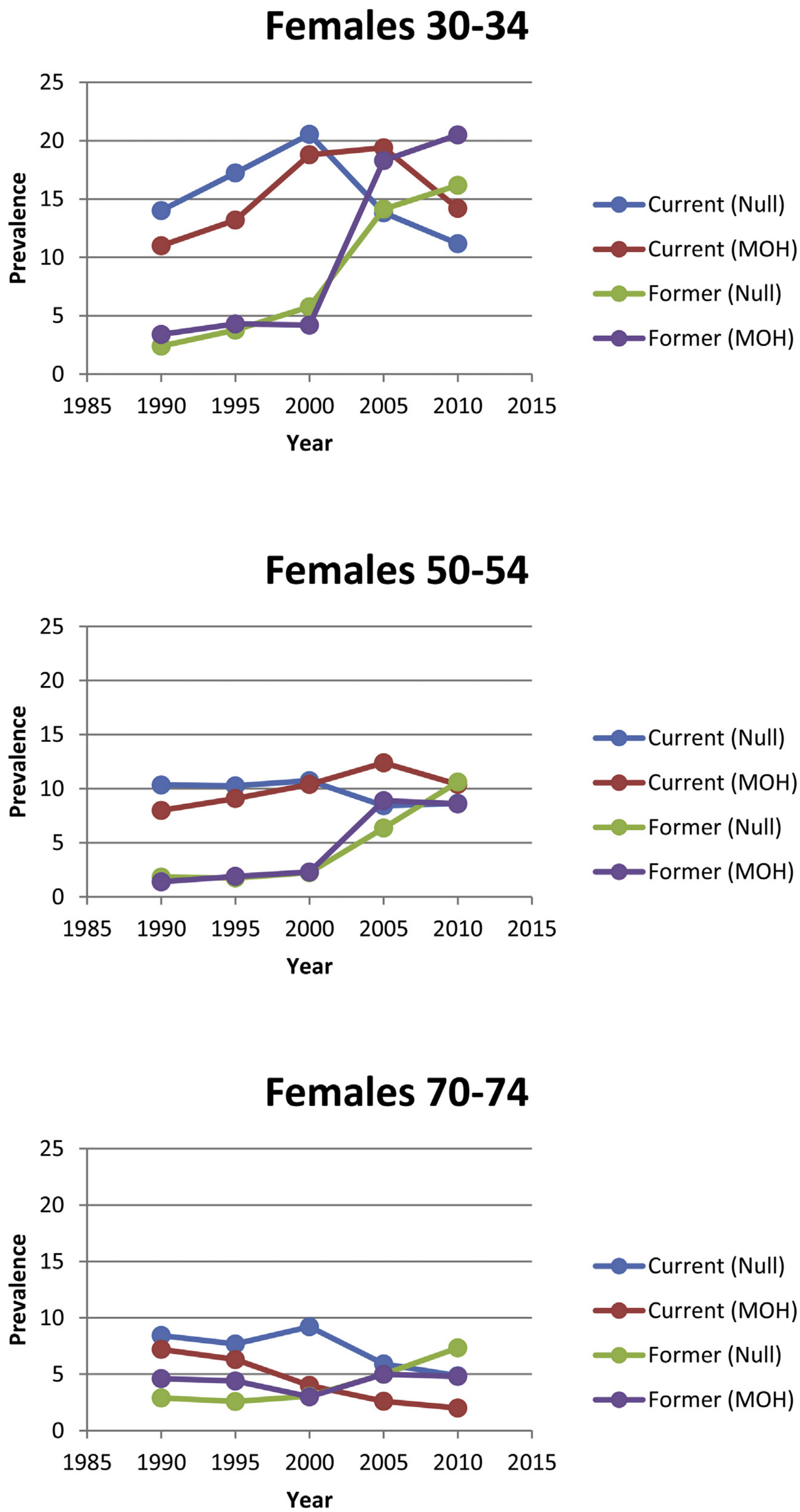

Fig. 2. Compares Null Scenario and Japan Ministry of Health estimates of current and former smoking prevalences for Japanese females at ages 30–34, 50–54, and 70–74 for the years 1990, 1995, 2000, 2005, and 2010.

Table 7 compares tobacco habits in each Alternative Scenario for each situation with those for which the TTPs were designed. Regarding the distributions in 2000, as expected, there were no tobacco users at all in Situation 1. While all the tobacco users were RRP users in Situation 2, they were all CC smokers in Situations 4 and 5. For Japan, in the situations involving RRP use, the percentage of tobacco users who were RRP users varied between 48.7% and 49.7%, as compared with "about 47%," while the percentage who were dual users varied from 7.7% to

Table 6
Prevalence of tobacco use in the Main situation for the U.S.

Sex	Age	Year	Null Scenario			Alternative Scenario				
			Never	Current	Former	Never	CC	RRP	Dual	Former
Male	30–34	1990	44.88	35.05	20.07	44.88	35.05	0.00	0.00	20.07
		1995	46.80	35.25	17.95	46.97	32.34	3.00	0.31	17.39
		2000	52.46	32.29	15.25	52.74	26.42	5.22	0.33	15.29
		2005	56.48	32.46	11.07	57.38	23.87	7.57	0.35	10.84
		2010	62.13	29.64	8.22	62.96	18.83	9.34	0.54	8.34
Male	50–54	1990	28.21	30.93	40.86	28.21	30.93	0.00	0.00	40.86
		1995	31.43	31.54	37.03	31.43	28.25	2.73	0.20	37.40
		2000	36.66	28.70	34.64	36.66	23.59	4.88	0.44	34.43
		2005	42.68	26.58	30.73	42.68	19.87	6.22	0.40	30.82
		2010	44.13	26.58	29.29	44.18	18.70	7.55	0.38	29.18
Male	70–74	1990	20.18	18.90	60.92	20.18	18.90	0.00	0.00	60.92
		1995	21.30	23.02	55.68	21.30	19.16	3.25	0.57	55.72
		2000	22.77	25.34	51.88	22.77	18.08	5.47	0.76	52.91
		2005	25.05	24.92	50.03	25.05	17.99	6.18	0.82	49.95
		2010	28.21	24.71	47.08	28.21	16.31	7.42	0.98	47.08
Female	30–34	1990	50.85	29.55	19.61	50.85	29.55	0.00	0.00	19.61
		1995	52.21	29.86	17.92	52.43	26.24	2.91	0.27	18.15
		2000	51.93	30.27	17.80	52.00	24.65	4.75	0.44	18.16
		2005	57.87	30.80	10.34	58.19	23.57	7.79	0.29	10.16
		2010	61.75	29.80	8.45	63.29	18.27	9.56	0.51	8.37
Female	50–54	1990	49.78	25.43	24.78	49.78	25.43	0.00	0.00	24.78
		1995	50.38	24.35	25.27	50.38	21.79	2.19	0.28	25.36
		2000	52.11	22.48	25.40	52.11	19.03	3.87	0.29	24.69
		2005	51.42	21.37	27.21	51.42	16.41	4.95	0.29	26.92
		2010	49.86	22.48	27.67	50.03	15.11	7.06	0.35	27.45
Female	70–74	1990	52.21	13.75	34.04	52.21	13.75	0.00	0.00	34.04
		1995	54.10	15.40	30.50	54.10	14.15	2.19	0.42	29.15
		2000	50.44	18.04	31.52	50.44	14.30	3.74	0.39	31.13
		2005	50.11	18.49	31.40	50.11	13.35	4.77	0.42	31.35
		2010	49.78	17.95	32.26	49.78	12.42	5.30	0.50	31.99

Note: In the Null Scenario, Current and Former refer to CC smoking.

8.8%, compared with "about 8%." For the U.S., in all the situations involving RRP use except Situation 8, the percentages of tobacco users who were RRP users varied between 17.0% and 18.2%, slightly higher than the "about 15%" specified, while the percentage of dual users varied between 1.7% and 2.5%, consistent with the "about 2%" specified. In Situation 8, the percentages of RRP only users and dual users were quite close to those planned.

As expected, the decline in prevalence of tobacco use between 1990 and 2005 was 100% in Situation 1. It is clear from Situations 2, 3, and 8 that there was a substantial decline in Japan, greater in males than females, but little change in prevalence in the U.S. Correspondence with the "about 30%" drop specified in the WHO Target situations and the "about 14%" drop in the WHO Projection situations was better for males than females and better where the RRP was not introduced. This reflects the difficulty of designing TTPs that satisfy both the WHO and the Main requirements and that for the U.S., where the TTPs were assumed to be the same in both sexes, development of the TTPs had mainly concentrated on obtaining a good correspondence for males. In any event, correspondence could never be perfect, given sampling variation.

For each sex, Table 8 presents estimated drops in deaths, separately for Japan and the U.S., associated with the different Alternative Scenarios. These are shown by disease and also for the four diseases combined. The results, which are expressed both as numbers and as a percentage of all tobacco-attributable deaths, are shown for the whole follow-up period 1990–2009. In considering these results, it should be noted that the distribution of the four diseases varies markedly between the countries. Compared with Japan, the proportion in the U.S. is much lower for stroke, much higher for COPD, and somewhat higher for IHD. Percentage drops in attributable deaths are always higher for IHD and stroke than for LC or COPD, due to the much shorter H for quitting.

In comparing the results for the different situations, we restrict attention in the first place to the results based on an effective dose of 0.2. As expected, the largest drops in deaths and in attributable deaths are seen where there is no further use of tobacco (Situation 1). Drops are also substantial where CC smoking is totally replaced by RRP use (Situation 2). For the four diseases combined, the drops in deaths relative to those for Situation 1 are about 73% in Japanese males and in American males and females and slightly higher, 78%, in Japanese females. This is consistent with baseline CC smokers having reductions in effective dose of 80% compared with 100%.

Expressed as a proportion of the corresponding drop for no further use of tobacco, drops in the Main situation are much greater for Japan (27% in males and 34% in females) than for the U.S. (about 8% in both sexes). This is because the assumed uptake of the RRP was much higher for Japan.

For the U.S., the drops in deaths compared with those in the Main situation are greater in the WHO Target situation and less in the WHO Projection situation. For Japan, the drops in the WHO Target situation are quite small, and those in the WHO Projection situation are negative, particularly for males. This is because in the Null Scenario, a substantial drop in prevalence was already seen. In males, for example, the drop in prevalence in the Null Scenario between 1990 and 2005 was 26.5%, almost as much as the WHO Target of about 30% and much greater than the WHO Projection of about 14%.

As expected, the drops in deaths in both countries for WHO Target with Main are greater than those for WHO Target or Main separately. Indeed, the drop in Situation 6 is quite close to the sum of the drops in the separate Situations 3 and 4 (e.g., American males 120,353 vs. 50,417 + 70,216 = 120,633). A similar conclusion can be reached comparing the drops for Situation 7 with the separate drops for Situations 3 and 5.

Table 7
Comparison of tobacco habits in the Alternative Scenario with those specified for each situation.

Situation		Country	Tobacco use distribution in 2000			Tobacco use in 2005[a]	
			CC	RRP	Dual	Prevalence	Drop %
Males							
1	No further use of tobacco	Japan	–	–	–	0.0	100.0
		U.S.	–	–	–	0.0	100.0
2	CC smoking totally replaced by RRP use	Japan	0.0	100.0	0.0	43.3	25.8
		U.S.	0.0	100.0	0.0	29.0	4.2
3	Main (about 47% RRP, 8% dual)	Japan	41.9	49.4	8.8	43.1	26.3
	Main (about 15% RRP, 2% dual)	U.S.	80.4	17.9	1.7	28.3	6.6
4	WHO Target (about 30% drop)	Japan	100.0	0.0	0.0	40.7	30.3
		U.S.	100.0	0.0	0.0	21.1	30.2
5	WHO Projection (about 14% drop)	Japan	100.0	0.0	0.0	50.4	13.7
		U.S.	100.0	0.0	0.0	25.8	14.7
6	WHO Target with Main	Japan	41.6	49.6	8.8	42.3	27.6
		U.S.	80.1	17.4	2.5	21.1	30.4
7	WHO Projection with Main	Japan	42.8	48.7	8.6	46.4	20.5
		U.S.	80.8	17.0	2.2	26.0	14.0
8	Extreme dual increase (about 5% RRP, 12.5% dual)	U.S.	81.3	6.2	12.5	28.5	5.9
Females							
1	No further use of tobacco	Japan	–	–	–	0.0	100.0
		U.S.	–	–	–	0.0	100.0
2	CC smoking totally replaced by RRP use	Japan	0.0	100.0	0.0	9.6	14.6
		U.S.	0.0	100.0	0.0	24.6	−1.7
3	Main (about 47% RRP, 8% dual)	Japan	43.4	48.8	7.7	9.8	13.3
	Main (about 15% RRP, 2% dual)	U.S.	80.1	18.2	1.7	24.1	0.3
4	WHO Target (about 30% drop)	Japan	100.0	0.0	0.0	7.7	31.9
		U.S.	100.0	0.0	0.0	18.1	25.1
5	WHO Projection (about 14% drop)	Japan	100.0	0.0	0.0	9.8	13.5
		U.S.	100.0	0.0	0.0	22.0	9.2
6	WHO Target with Main	Japan	42.5	49.7	7.8	8.9	21.2
		U.S.	79.9	17.7	2.4	18.1	25.0
7	WHO Projection with Main	Japan	43.4	48.8	7.7	9.8	13.3
		U.S.	80.7	17.2	2.1	22.3	7.6
8	Extreme dual increase (about 5% RRP, 12.5% dual)	U.S.	81.2	6.5	12.3	24.3	−0.4

[a] The initial prevalences of CC smoking in 1990 were Japanese males 58.5%, Japanese females 11.3%, American males 30.3%, American females 24.2%.

As expected, the drops in deaths in the U.S. for the extreme dual use situation are less than for the Main model due to the greater proportion of dual users among those who use RRP. However, the drop in deaths still exceeds that in the WHO Projection situation.

The comparisons of the drops in deaths in the different situations described above were based on the results for an effective dose, F, of 0.2 for those situations where the RRP was introduced. As expected, assuming a lower F (0.1) increased the drops, and assuming a higher F (0.3) decreased them. For F = 0.1, the drops for Japan, compared with Situation 1, were 86% for males and 89% for females for Situation 2 and 31% for males and 38% for females for Situation 3.

In all the relevant situations, the drops were approximately linearly related to F over the range studied. For Situations 2 and 3, the drops in deaths, expressed per 10% reduction in F, were quite similar for F = 0.1, 0.2, or 0.3. Thus, for example, for Japan, the overall drops in deaths for the four diseases in males were 74,071 for a 90% reduction (F = 0.1), 64,481 for an 80% reduction (F = 0.2), and 55,247 for a 70% reduction (F = 0.3) for Situation 3, reductions per 10% drop of 8,230, 8,060, and 7,890, respectively. For females, the corresponding reductions are 6,384, 6,302, and 6,207. This suggests approximate linearity down to a drop of zero for a 0% reduction (F = 1). This is not so where the WHO Target or Projection are combined with the Main, as the drops are not zero where F = 1, equivalent to the simple WHO Target or Projection situations.

For the Main situation, Table 9 similarly shows results for the years 1995, 2000, 2005, and 2009. In both countries and in both sexes, the drop in deaths and the percentage drop in attributable deaths clearly increased with time. This reflects the time taken for the population to take up RRP as well as the time needed for the resultant decline in risk to take place.

Table 10 presents data on YLS in the Alternative Scenario, corresponding to the data on drops in mortality shown in Table 8. The rank order of the different situations is very similar to that seen there. Thus, in each country and in both sexes, the greatest health impact is seen in Situation 1, with Situations 2 and then 7 being next best and Situation 6 being the worst. The reduction in risk in the Main situation, as a proportion of that in Situation 1, is clearly much greater for Japan than for the U.S. due to the much higher assumed uptake of the RRP.

The results presented in Tables 8–10 all relate to analyses conducted without adjustment for the difference in population size between Scenarios. Compared with the unadjusted estimates of drops in deaths for the four diseases in Japanese males for Situations 1, 2 (F = 0.2), and 6 (F = 0.2) of 236,221, 172,103, and 66,649, respectively, shown in Table 8, the corresponding adjusted estimates were 234,793, 170,787, and 66,112, lower by 0.6%, 0.8%, and 0.8%, respectively. For the corresponding results for the U.S., the adjusted estimates were lower by 1.2%, 1.4%, and 1.5%. These examples are consistent with the modest effect of adjustment noted earlier (Lee et al., 2017).

4. Discussion

Quitting all tobacco use clearly has the greatest population health impact. If tobacco use were to disappear completely at the start of the follow-up period, we estimate a reduction for Japan of 269,916 smoking-attributable deaths for males and females combined over 20 years. This reduction represents 37.3% of the estimated total of 724,601 attributable deaths that would occur, given existing trends in smoking and no introduction of an RRP. That it is not a higher proportion reflects the long-term excess disease risk that remains for many years after quitting.

Table 8
Drops in deaths associated with the Alternative Scenario over the whole follow-up period in Japan and the U.S. in the different situations.

	Situation	Country	F[a]	Drop in deaths					% drop in attributable deaths				
				LC	IHD	Stroke	COPD	Four diseases	LC	IHD	Stroke	COPD	Four diseases
Males													
1	No further use of tobacco	Japan	–	75293	79815	73185	7927	236221	22.88	55.84	51.92	20.14	36.21
		U.S.	–	143299	354604	46979	65325	610207	12.30	54.72	54.68	16.60	26.62
2	CC Smoking totally replaced by RRP use	Japan	0.1	64739	67283	63587	6941	202550	19.67	47.07	45.11	17.63	31.05
			0.2	55074	56392	54636	6001	172103	16.73	39.45	38.76	15.25	26.38
			0.3	46172	46753	46253	5103	144281	14.03	32.71	32.82	12.97	22.12
		U.S.	0.1	119393	305687	41252	56927	523259	10.25	47.17	48.01	14.47	22.83
			0.2	98887	260737	35775	49008	444407	8.49	40.24	41.64	12.46	19.39
			0.3	80998	219170	30528	41524	372220	6.95	33.82	35.53	10.55	16.24
3	Main	Japan	0.1	22507	24746	24374	2443	74071	6.85	17.33	17.33	6.22	11.37
			0.2	19620	21418	21301	2142	64481	5.97	15.00	15.14	5.46	9.90
			0.3	16826	18257	18318	1847	55247	5.12	12.79	13.02	4.70	8.48
		U.S.	0.1	11402	33845	5120	7088	57455	0.98	5.24	5.98	1.81	2.51
			0.2	9980	29703	4506	6228	50417	0.86	4.60	5.26	1.59	2.20
			0.3	8578	25602	3895	5375	43451	0.74	3.96	4.55	1.37	1.90
4	WHO Target	Japan	–	1549	1254	1413	214	4431	0.47	0.88	1.00	0.55	0.68
		U.S.	–	14256	40777	6199	8984	70216	1.23	6.31	7.24	2.29	3.07
5	WHO Projection	Japan	–	−6315	−4883	−5676	−941	−17815	−1.92	−3.42	−4.03	−2.40	−2.74
		U.S.	–	4675	12272	1972	3252	22171	0.40	1.90	2.30	0.83	0.97
6	WHO Target with Main	Japan	0.1	23280	25360	25015	2550	76205	7.08	17.76	17.78	6.50	11.70
			0.2	20404	22036	21956	2252	66649	6.21	15.44	15.61	5.74	10.23
			0.3	17622	18879	18986	1959	57447	5.36	13.22	13.50	4.99	8.82
		U.S.	0.1	25758	74044	10970	15439	126213	2.21	11.45	12.81	3.93	5.52
			0.2	24546	70561	10478	14768	120353	2.11	10.92	12.24	3.76	5.26
			0.3	23347	67107	9988	14101	114544	2.01	10.38	11.67	3.59	5.01
7	WHO Projection with Main	Japan	0.1	19143	22225	21674	1963	65005	5.82	15.57	15.41	5.00	9.98
			0.2	16230	18889	18558	1653	55331	4.94	13.23	13.19	4.21	8.49
			0.3	13414	15719	15533	1350	46016	4.08	11.01	11.04	3.44	7.06
		U.S.	0.1	15378	44724	6748	9516	76366	1.32	6.92	7.88	2.42	3.34
			0.2	14126	41010	6207	8787	70131	1.21	6.34	7.25	2.24	3.06
			0.3	12889	37331	5670	8064	63954	1.11	5.78	6.62	2.05	2.79
8	Extreme dual use increase	U.S.	0.1	7299	21731	3310	4546	36886	0.63	3.36	3.87	1.16	1.61
			0.2	6330	18935	2889	3947	32100	0.54	2.93	3.37	1.01	1.40
			0.3	5370	16155	2469	3351	27345	0.46	2.50	2.88	0.85	1.20
Females													
1	No further use of tobacco	Japan	–	13218	8071	11634	772	33695	37.56	56.55	57.80	29.47	46.66
		U.S.	–	115413	123126	34492	62596	335627	16.19	52.65	56.02	21.05	25.71
2	CC Smoking totally replaced by RRP use	Japan	0.1	11735	7166	10378	690	29969	33.35	50.21	51.56	26.31	41.50
			0.2	10289	6286	9143	608	26325	29.24	44.04	45.42	23.20	36.45
			0.3	8879	5427	7926	527	22760	25.23	38.02	39.38	20.12	31.52
		U.S.	0.1	96848	107366	30402	54753	289369	13.59	45.91	49.38	18.41	22.16
			0.2	80674	92537	26460	47295	246966	11.32	39.57	42.98	15.90	18.92
			0.3	66387	78526	22655	40192	207760	9.31	33.58	36.80	13.51	15.91
3	Main	Japan	0.1	4955	3103	4468	287	12814	14.08	21.73	22.18	10.96	17.74
			0.2	4383	2743	3958	255	11339	12.45	19.20	19.65	9.72	15.69
			0.3	3818	2386	3452	223	9879	10.85	16.71	17.14	8.49	13.67
		U.S.	0.1	9117	12258	3768	6431	31573	1.28	5.25	6.14	2.17	2.42
			0.2	7979	10771	3319	5637	27706	1.12	4.62	5.41	1.90	2.13
			0.3	6856	9295	2873	4849	23873	0.96	3.98	4.68	1.63	1.83
4	WHO Target	Japan	–	619	411	584	35	1649	1.76	2.88	2.90	1.34	2.28
		U.S.	–	11978	15370	4695	8617	40660	1.68	6.59	7.65	2.90	3.12
5	WHO Projection	Japan	–	−29	−19	−17	−3	−69	−0.08	−0.13	−0.09	−0.13	−0.10
		U.S.	–	3424	4450	1406	2573	11854	0.48	1.91	2.29	0.87	0.91
6	WHO Target with Main	Japan	0.1	5216	3270	4694	303	13482	14.82	22.89	23.30	11.55	18.66
			0.2	4649	2913	4189	271	12022	13.21	20.39	20.80	10.33	16.64
			0.3	4089	2560	3689	239	10577	11.62	17.92	18.31	9.12	14.64
		U.S.	0.1	21074	26765	8082	14586	70506	2.96	11.47	13.17	4.91	5.41
			0.2	20089	25548	7723	13948	67308	2.82	10.95	12.58	4.70	5.16
			0.3	19116	24339	7365	13314	64133	2.68	10.43	12.00	4.49	4.92
7	WHO Projection with Main	Japan	0.1	4955	3103	4468	287	12814	14.08	21.73	22.18	10.96	17.74
			0.2	4383	2743	3958	255	11339	12.45	19.20	19.65	9.72	15.69
			0.3	3818	2386	3452	223	9879	10.85	16.71	17.14	8.49	13.67

(*continued on next page*)

Table 8 (*continued*)

	Situation	Country	F[a]	Drop in deaths					% drop in attributable deaths				
				LC	IHD	Stroke	COPD	Four diseases	LC	IHD	Stroke	COPD	Four diseases
		U.S.	0.1	12405	16239	4961	8758	42364	1.74	6.96	8.08	2.95	3.25
			0.2	11385	14919	4564	8065	38933	1.60	6.40	7.43	2.72	2.99
			0.3	10377	13608	4168	7376	35529	1.46	5.83	6.79	2.49	2.73
8	Extreme dual use increase	U.S.	0.1	5706	7801	2406	3983	19897	0.80	3.34	3.92	1.34	1.53
			0.2	4918	6771	2095	3421	17205	0.69	2.90	3.41	1.15	1.32
			0.3	4137	5746	1784	2861	14528	0.58	2.46	2.91	0.96	1.11

[a] Assumed effective dose for RRP compared with CC. For dual use, effective dose taken as (1 + F)/2.

Table 9
Drops in mortality in the Main situation by year in Japan and the U.S.[a]

Country	Sex	Year	Drop in deaths					% drop in attributable deaths				
			LC	IHD	Stroke	COPD	Four diseases	LC	IHD	Stroke	COPD	Four diseases
Japan	Male	1995	286	431	566	43	1326	1.86	5.35	6.77	1.91	3.90
		2000	950	1151	1302	116	3518	5.52	14.81	17.93	5.37	10.22
		2005	1754	1892	1718	196	5560	9.62	24.65	27.51	8.96	16.19
		2009	2325	2147	1757	223	6452	13.25	32.03	33.99	11.84	20.61
	Female	1995	74	74	126	7	280	4.36	8.28	10.26	3.71	7.02
		2000	232	162	264	14	672	12.52	21.09	25.02	11.23	17.67
		2005	382	224	305	22	933	20.10	32.24	36.09	18.14	26.20
		2009	472	221	268	22	982	25.56	39.13	41.38	23.19	31.16
U.S.	Male	1995	129	497	81	77	783	0.21	1.47	1.78	0.39	0.66
		2000	464	1600	241	293	2598	0.80	4.72	5.52	1.47	2.24
		2005	903	2582	376	572	4433	1.64	8.71	9.34	2.88	4.08
		2009	1281	3239	505	808	5833	2.46	12.14	13.02	4.13	5.71
	Female	1995	99	174	58	68	400	0.29	1.43	1.79	0.50	0.63
		2000	335	576	180	231	1321	0.91	4.56	5.55	1.46	1.94
		2005	737	958	286	535	2517	1.97	8.83	9.81	3.24	3.72
		2009	1064	1131	351	774	3320	2.88	12.10	13.04	4.57	5.04

[a] The results are for an effective dose for RRP compared with CC of 0.2.

A substantial proportion of this reduction would occur if, instead of quitting, CC smoking in Japan were totally replaced by RRP use at the start of follow-up, with estimated reductions, for the sexes combined, ranging from 232,519 deaths if the RRP were assumed to have 90% of the effect of quitting (F = 0.1) to 167,041 deaths if it were assumed to have 70% of the effect (F = 0.3).

In practice, neither of these situations would occur in real life, and the reductions in deaths where the RRP is introduced at baseline, with uptake rates based on experience following the introduction of *IQOS* three years ago in Japan, are more relevant. Here, the reductions for this "Main" situation, for the sexes combined, range from 86,885 deaths for F = 0.1 to 65,126 deaths for F = 0.3. These reductions, which represent from 12.0% to 9.0% of the total of 724,601 attributable deaths noted above, are less than those in the extreme situations considered but are nevertheless substantial and relevant. Expressed as a percentage of attributable deaths, the proportions are larger than those that we estimated for the U.S., based on the lower uptake rate of RRPs assumed there.

For Japan, the effect of introducing WHO's Target of an approximately 30% reduction in smoking prevalence over a 15-year period would be much less, as the reduction in prevalence that would be expected in Japan, based on the TTPs appropriate for that country, is almost as great and is greater than for the WHO's projected reduction of about 14%. As a result, reductions in attributable deaths in Situation 6 (WHO Target + Main) are only slightly higher than those in the Main situation, and those in Situation 7 (WHO Projection + Main) are lower.

Compared with the results for the U.S., the percentage drops in attributable deaths for Japan are higher in many of the situations (see Table 8). One reason for this, relevant particularly to Situations 1 and 2, is the much higher proportion in Japan of deaths from IHD and stroke, causes of death for which the RR declines much more rapidly upon quitting. Also, in Situation 3, the rate of uptake of the RRP is assumed to be much higher in Japan than in the U.S. Here, the percentage drops in attributable deaths for Japan are estimated to be more than four times higher for males and more than seven times higher for females than those estimated for the U.S. In the WHO Situations 4 and 5, the percentage drops in Japan are, in contrast, lower than in the U.S. This is because the downward trends in smoking prevalence that have actually occurred are greater in Japan than in the U.S. Despite this, in the combination Situations 6 and 7, the percentage drops in Japan remain clearly higher than in the U.S.

The results we present for the U.S. are quite similar to those reported earlier (Djurdjevic et al., 2018), based on simulations of 10,000 rather than 100,000 individuals. Their discussion section commented on various aspects of the modelling, which are also relevant to Japan, making points summarized briefly here. One is the need to validate the NEM further, based on large epidemiological studies that collect extensive information on changes in tobacco use over time.

Another point is that the model is limited in accounting for all forms of tobacco use. Not considering smokeless tobacco, nicotine replacement therapy, or e-cigarettes as any health effects they have are minor compared with those from cigarettes. While our modelling effectively assumes that cigar and pipe smoking have the same risk as cigarettes, any error from this assumption is likely to be unimportant, because cigarette smokers form the vast majority of all smokers in both Japan and the U.S.

Ignoring environmental tobacco smoke exposure is also reasonable, as any health effects from it are much less than those from smoking. Our

Table 10
Years of life saved (thousands) over the whole follow-up period in Japan and U.S. in the different situations.

	Situation	Country	F[a]	Males					Females				
				LC	IHD	Stroke	COPD	Four diseases	LC	IHD	Stroke	COPD	Four diseases
1	No further use of tobacco	Japan	–	659	1290	1081	26	3056	130	114	183	2.9	431
		U.S.	–	1627	6242	760	470	9099	1252	1878	568	442	4140
2	CC Smoking totally replaced by RRP use	Japan	0.1	560	1060	929	23	2572	115	101	163	2.6	382
			0.2	472	868	790	20	2151	101	88	143	2.3	334
			0.3	393	704	662	17	1778	86	75	124	2.0	287
		U.S.	0.1	1330	5314	664	408	7716	1031	1616	498	385	3531
			0.2	1085	4480	572	350	6487	846	1376	431	332	2986
			0.3	878	3725	486	296	5384	688	1155	368	281	2492
3	Main	Japan	0.1	197	388	351	8.4	944	47	44	69	1.0	161
			0.2	171	332	306	7.4	816	42	39	61	0.9	142
			0.3	146	281	262	6.4	695	36	34	53	0.8	124
		U.S.	0.1	108	558	76	44	785	88	181	59	42	370
			0.2	94	490	67	38	689	77	159	52	37	326
			0.3	81	422	58	33	594	66	137	46	32	281
4	WHO Target	Japan	–	8.1	13	14	0.5	36	6.0	6.8	9.7	0.1	23
		U.S.	–	128	656	89	52	925	106	215	70	52	442
5	WHO Projection	Japan	–	−30	−47	−50	−2	−129	−0.03	−0.1	−0.02	−0.003	−0.1
		U.S.	–	35	182	26	15	259	30	63	22	15	130
6	WHO Target with Main	Japan	0.1	201	395	358	8.7	962	50	47	72	1.1	170
			0.2	175	340	312	7.6	834	44	42	65	1.0	151
			0.3	150	288	268	6.6	713	39	36	57	0.9	133
		U.S.	0.1	244	1218	162	95	1718	194	383	122	91	791
			0.2	231	1158	154	87	1633	185	365	117	87	752
			0.3	219	1098	146	86	1549	175	346	111	83	715
7	WHO Projection with Main	Japan	0.1	181	361	326	7.4	875	47	44	69	1,0	161
			0.2	155	306	280	6.4	747	42	39	61	0.9	142
			0.3	130	255	236	5.3	627	36	34	53	0.8	124
		U.S.	0.1	143	728	99	57	1027	115	233	76	56	479
			0.2	130	664	90	53	938	105	213	69	51	439
			0.3	118	602	82	48	850	96	193	63	47	399
8	Extreme dual use increase	U.S.	0.1	70	355	50	28	503	56	114	39	28	236
			0.2	61	311	44	25	440	49	99	34	24	206
			0.3	52	267	38	21	377	42	85	29	21	177

estimates of deaths saved may also be in error if those who switch from smoking to RRP use tend to be atypical in their smoking habits in some ways or change their distribution of other risk factors. However, none of these reservations would affect our general conclusion that the introduction of an RRP could substantially reduce smoking-associated deaths.

This earlier paper (Djurdjevic et al., 2018) also made two points that suggest that the benefit of RRP introduction may be underestimated in our calculations. One point was our restriction to the four major smoking-associated diseases in the absence of reliable data on RR and H for other diseases associated with smoking. We estimated earlier (Weitkunat et al., 2015) that smoking-attributable deaths from the four diseases form about two-thirds of the total, so increasing our estimates of deaths saved by about 50% seems likely to give a reasonably accurate estimate for all smoking-related diseases combined. The other point is that our analyses limited attention to a 20-year follow up. It is clear from Table 9 that the percentage drop in attributable deaths increases with time of follow up, so that the estimated benefit of RRP introduction would be greater for a longer follow up.

In an earlier paper (Lee et al., 2017), we presented detailed sensitivity analyses of the effect of differing assumptions on the population health impact of introducing a RRP into the U.S. Apart from varying, as we have, the effective dose for RRP use vs. CC smoking, other assumed values were also varied across plausible ranges, including the effective dose factor for dual use, the RR and H, the relative frequency of initiation and re-initiation rates, and the initiation and switching rates. The two most important sources of variation identified were the effective dose for RRP use compared with CC smoking and the rate of switching to the RRP, with the next two most important sources being the rate of switching to CCs and the rate of quitting from RRP or dual use. While we have not repeated all these analyses for Japan, we believe that had we done so, the general conclusions would have been the same. That paper (Lee et al., 2017) also noted that the estimated drops in deaths associated with RRP introduction would be reduced but not eliminated by plausible increases in re-initiation rates or higher estimates of CC consumption by dual users, or by decreased quitting by smokers, and we believe that this conclusion would also hold for Japan.

Overall, we believe that the results that we present here give a good insight into how much introduction of a RRP might affect the distribution of tobacco use in Japan and the number of deaths that are attributable to tobacco use.

5. Conclusions

The introduction of a RRP into Japan, at a rate suggested by three years of experience with the heat-not-burn product *IQOS*, will lead to a substantial reduction in tobacco-related deaths.

Software

The software used to generate the analyses described in this paper will become available on the Philip Morris International website.

Conflicts of interest

SD, RW, and GB are employees of Philip Morris International. PNL, director of P.N. Lee Statistics and Computing Ltd., is an independent consultant to a number of tobacco companies.

Acknowledgements

We thank the following people for their generous assistance. Mrs Emi Konishi for providing us with Japanese relevant data and translations. Dr. J.S. Fry and John F. Hamling for assistance in running the software (which they developed) and for checking some of the results obtained. Mrs. Y. Cooper and Mrs. D. Morris for typing the various drafts of this report, and we thank Philip Morris International for financial support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yrtph.2018.10.010.

Transparency document

Transparency document related to this article can be found online at https://doi.org/10.1016/j.yrtph.2018.10.010.

References

Djurdjevic, S., Lee, P.N., Weitkunat, R., Sponsiello-Wang, Z., Lüdicke, F., Baker, G., 2018. Modeling the population health impact of introducing a modified risk tobacco product into the U.S. market. Warn. J. Abbreviation Not Set 6 (2), 47. https://doi.org/10.3390/healthcare6020047.

Forey, B., Hamling, J., Lee, P., Wald, N. (Eds.), 2002. International Smoking Statistics. A Collection of Historical Data from 30 Economically Developed Countries, second ed. Wolfson Institute of Preventive Medicine and Oxford University Press, London and Oxford Errata available at: www.pnlee.co.uk/ISS2.htm Data after 1995 by personal communication from the authors.

Forey, B., Lee, P., 2002. Estimation of Sex-specific Smoking Statistics by Standardized Age Groups and Time Periods. Supplement 1 to International Smoking Statistics, a Collection of Historical Data from 30 Economically Developed Countries, second ed. P N Lee Statistics and Computing Ltd, Sutton, Surrey Available: www.pnlee.co.uk/Reports.htm. file:\h:\smokstat\newpub1\suppl [Download ISS2suppl1 FOREY2002C].

Gardner, J.W., Sanborn, J.S., 1990. Years of potential life lost (YPLL)–what does it measure? Epidemiology 1 (4), 322–329.

Langer, P., et al., 2018. Prevalence and patterns of tobacco product use in Japan: first-year results of a repeated cross-sectional survey. In: Proceedings from 4th International Conference on Public Health (ICOPH 2018). July 2018; Bangkok, Thailand, ISBN 978-955-3605-05-4.

Lee, P.N., Forey, B.A., Fry, J.S., Hamling, J.S., Hamling, J.F., Sanders, E.B., Carchman, R.A., 2009. Does use of flue-cured rather than blended cigarettes affect international variation in mortality from lung cancer and COPD? Available: Supplementary material available at. Inhal. Toxicol. 21 (5), 404–430. :[Download LEE2008L]. www.pnlee.co.uk/Reports.htm.

Lee, P.N., Forey, B.A., Thornton, A.J., Coombs, K.J., 2018. The Relationship of Cigarette Smoking in Japan to Lung Cancer, COPD, Ischemic Heart Disease and Stroke: a Systematic Review [version 1; Referees: Awaiting Peer Review], vol. 7. F1000Research, pp. 204. https://doi.org/10.12688/f1000research.14002.1.

Lee, P.N., Fry, J.S., Hamling, J.F., Sponsiello-Wang, Z., Baker, G., Weitkunat, R., 2017. Estimating the effect of differing assumptions on the population health impact of introducing a Reduced Risk Tobacco Product in the U.S.A. Regul. Toxicol. Pharmacol. 88, 192–213. https://doi.org/10.1016/j.yrtph.2017.06.009.

Martin, F., Vuillaume, G., Baker, G., Sponsiello-Wang, Z., Ricci, P.F., Lüdicke, F., Weitkunat, R., 2018. Quantifying the risk-reduction potential of new Modified Risk Tobacco Products. Regul. Toxicol. Pharmacol. 92, 358–369. https://doi.org/10.1016/j.yrtph.2017.12.011.

United Nations Department of Economic and Social Affairs, 2013. World population prospects: the 2012 revision. Excel tables - population data. United Nations, Department of Economic and Social Affairs, Population Division, Population Estimates and Projections Section. Available: http://esa.un.org/wpp/Excel-Data/population.htm. http://esa.un.org/unpd/wpp/Documentation/pdf/WPP2012_HIGHLIGHTS.pdf. http://www.un.org/en/development/desa/population/publications/pdf/trends/WPP2012_Wallchart.pdf.

United Nations Department of Economic and Social Affairs Population Division, 2015. World Population Prospects: the 2015 Revision. United Nations Available: http://esa.un.org/unpd/wpp/Download/Standard/Population/.

Weitkunat, R., Lee, P.N., Baker, G., Sponsiello-Wang, Z., González-Zuloeta Ladd, A.M., Lüdicke, F., 2015. A novel approach to assess the population health impact of introducing a modified risk tobacco product. Regul. Toxicol. Pharmacol. 72, 87–93. https://doi.org/10.1016/j.yrtph.2015.03.011.

World Health Organization, 2015. WHO Study Group on Tobacco Product Regulation : Report on the Scienfific Basis of Tobacco Product Regulation. Fifth Report of a WHO Study Group. WHO Press, Geneva WHO Technical Report Series 989. Available: http://apps.who.int/iris/bitstream/10665/161512/1/9789241209892.pdf?ua=1&ua=1.