Nicotine & Tobacco Research, 2017, 1277–1283
doi:10.1093/ntr/ntx070
Original investigation
Received May 19, 2016; Editorial Decision March 20, 2017; Accepted March 24, 2017

Original investigation

Population Modeling of Modified Risk Tobacco Products Accounting for Smoking Reduction and Gradual Transitions of Relative Risk

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Abstract

Introduction: As suggested by the Food and Drug Administration (FDA) Modified Risk Tobacco Product (MRTP) Applications Draft Guidance, we developed a statistical model based on public data to explore the effect on population mortality of an MRTP resulting in reduced conventional cigarette smoking. Many cigarette smokers who try an MRTP persist as dual users while smoking fewer conventional cigarettes per day (CPD). Lower-CPD smokers have lower mortality risk based on large cohort studies. However, with little data on the effect of smoking reduction on mortality, predictive modeling is needed.

Methods: We generalize prior assumptions of gradual, exponential decay of Excess Risk (ER) of death, relative to never-smokers, after quitting or reducing CPD. The same age-dependent slopes are applied to all transitions, including initiation to conventional cigarettes and to a second product (MRTP). A Monte Carlo simulation model generates random individual product use histories, including CPD, to project cumulative deaths through 2060 in a population with versus without the MRTP. Transitions are modeled to and from dual use, which affects CPD and cigarette quit rates, and to MRTP use only.

Results: Results in a hypothetical scenario showed high sensitivity of long-run mortality to CPD reduction levels and moderate sensitivity to ER transition rates.

Conclusions: Models to project population effects of an MRTP should account for possible mortality effects of reduced smoking among dual users. In addition, studies should follow dual-user CPD histories and quit rates over long time periods to clarify long-term usage patterns and thereby improve health impact projections.

Implications: We simulated mortality effects of a hypothetical MRTP accounting for cigarette smoking reduction by smokers who add MRTP use. Data on relative mortality risk versus CPD suggest that this reduction may have a substantial effect on mortality rates, unaccounted for in other models. This effect is weighed with additional hypothetical effects in an example.

Introduction

The US FDA's Center for Tobacco Products (CTP) regulates tobacco products to protect public health using a "public health standard."[1] For new tobacco products, this standard requires the CTP to determine the likelihood of risk reduction to individual users and to the population as a whole. Models have been used to project tobacco use and health impacts in populations for over a decade[1(App. 15.1)] and are now being extended to potential Modified Risk Tobacco Products (MRTPs)[2–6] as suggested by the FDA's draft guidance on MRTP applications.[7]

These new products might reduce mortality among smokers who switch to them. However, risks being debated include extended dual use rather than complete switching, increased initiation to tobacco products (including the MRTP), relapse of former smokers to the MRTP, role as a gateway to conventional cigarette smoking, and long-term health risks of the MRTP. We developed a two-product Monte Carlo simulation model to explore possible population impacts of an MRTP in addition to conventional cigarettes. The cigarette sub-model incorporates effects on mortality risk of age, sex, time since quitting for former smokers, and usage level measured by cigarettes per day (CPD). The MRTP sub-model incorporates an additional risk of death from MRTP use. It allows transitions to and from dual use and the MRTP alone, and effects of dual use on CPD and cigarette quit rates. A random sample of the US adult population is simulated from 2012 to 2060, following individual histories of use of tobacco products, from which tobacco use and mortality statistics are calculated.

Many smokers taking up electronic cigarettes (e-cigs) become dual users, continuing conventional cigarette use at a lower level.[8] Thus, key uncertainties for e-cigs and other potential MRTPs are the durations and patterns of dual use and the health impacts of smoking reduction. This work explores the potential effects on mortality of reduced CPD among dual users. In addition, a consistent approach to describing the change of mortality risk after CPD reduction, or any other change in tobacco product use, is presented.

Literature Relating Mortality to Cigarette Use Level and Reduction

Among smokers, lower mortality rates at lower cigarette use levels measured by CPD are well documented.[9–13] Mortality rates are often expressed as relative risk (RR) of death, relative to never-smokers. RR has been calculated as a function of CPD, from 0 (never-smokers) through 40 or more CPD (Figure 1). Light or intermittent smoking carries a much higher risk than never smoking,[14] and in general RR appears to increase more slowly at higher CPD levels. After smokers quit completely, a slow decrease in RR over time is seen in analysis of survey data.[2(App. S2),9,10,13,15] Using Cancer Prevention Survey II (CPS-II) data, Mendez and Warner[15] modeled this decrease as a function of time since quitting, age, and sex, with RR gradually decreasing toward 1, the never-smoker level (Figure 2).

However, the effect on mortality of reducing CPD is much less studied and is controversial.[16] A study of about 50 000 Norwegians failed to find a significant reduction in the risk of premature death among heavy smokers who reduced their cigarette consumption by >50%.[17] A systematic review of 25 studies found the data too limited to draw conclusions about mortality effects but suggested small improvements of cardiovascular risk factors, respiratory symptoms, and incidences of lung cancer.[18] In two long-term cohort studies in Scotland, results were inconsistent, with some reduction in mortality among former heavy smokers in only one of the studies.[19] On the other hand, in a long-term cohort study of 4633 Israeli working men, a survival benefit was found for reduced smoking, especially among former heavy smokers and for cardiovascular disease mortality.[20] In addition, a review of 14 studies found significant evidence that cigarette smokers who reduce their consumption have a lower risk of lung cancer and all-cause mortality, though all studies had limitations.[21] In addition, studies of dual users of conventional cigarettes and snus (Swedish-type moist snuff) provide indirect evidence of the mortality benefits of reducing CPD, with generally lower RRs among dual users than smokers, presumably due to reduced smoking.[22]

This inconsistent evidence for mortality effects of smoking reduction is not surprising given the additional variables involved. Comparisons usually depend on at least two levels of cigarette use (often varying by individual) and at least three time periods of varying lengths: pre-smoking, higher-CPD, and lower-CPD. Epidemiological studies typically measure smoking on only two occasions. Moreover, it is implicitly assumed that any smoking reduction at the second occasion has been maintained throughout the follow-up period, though in fact smoking reduction may be unsuccessful or variable over time. Also, both the RRs for smokers and the benefits of quitting tend to decrease with age (Figure 2), so similar age effects with reduced smoking are plausible.

Ideally, mortality risk calculations would account for entire individual tobacco use histories. For example, a "tobacco exposure index" was posited in a differential equation model assuming

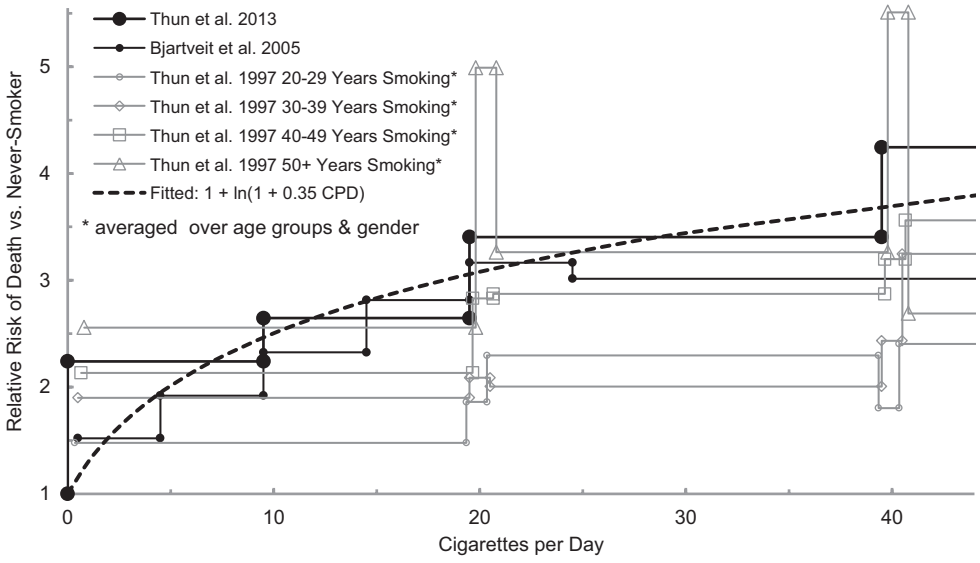

Figure 1. Relative risk of death versus cigarettes per day, and fitted curve. Relative risk (RR) increases with CPD, though RRs vary by study and may increase with years smoking. Differences in sex were small and therefore ignored. A logarithmic curve served to fit the data.

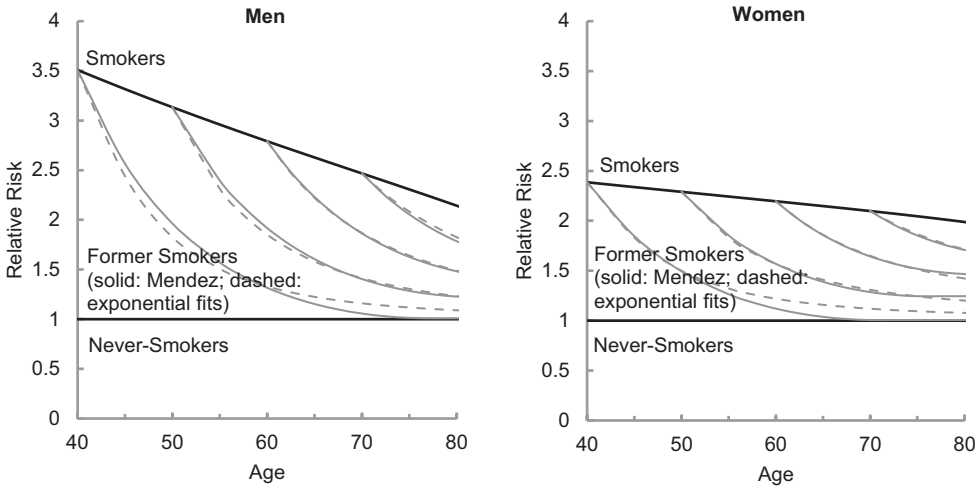

Figure 2. Modeling of former smoker relative risks by age, age quit, and sex.[15] Relative risks of death decrease with age (though absolute risks still increase sharply with age) and decay approximately exponentially after quitting. Decay rates are slower at older ages. The same exponential fits were used for men and women due to negligible differences.

an age-dependent ability to purge accumulating tobacco toxins.[23] However, the data available to estimate the model was limited to a registry of male military veteran twins, making validation and generalization to other populations difficult. A complex set of models was developed for the National Cancer Institute's Cancer Intervention and Surveillance Modeling Network (CISNET), which generate individual smoking histories and simulate consequent lung cancer mortality; however, these models were intended to explain historical lung cancer rates and deaths rather than future, all-cause deaths.[24–27]

Excess risk (ER, defined as RR-1) has been modeled as decaying exponentially after a smoker quits, toward the zero value of a never-smoker.[4,28,29] We generalize this decay to an exponential approach from any initial ER level toward any new level, determined by cigarette "dose" (CPD), or equivalent cigarette dose for an MRTP.[29] The effect of smoking reduction on mortality is captured by combining a fit of the CPD-RR relationship (Figure 1) with exponential decay slopes for ER (Figure 2).

Methods

We posit that a change in tobacco product use produces a change in equilibrium RR of death, and that RR changes exponentially toward its new equilibrium. This applies not just after cigarette cessation but after any change in tobacco product use: initiation, addition, change in use level, or cessation. For simplicity we work in terms of ER, defined as RR-1. After a smoker quits, we assume ER decays exponentially from its current value ER(0) to its value after time t: ER(0) exp($-k\,t$), where k is the decay slope, or equivalently ln(2)/k is the half-life. Thus ER(t) approaches 0 as an asymptote. Generalizing this asymptote to any equilibrium value ER_{eq} leads to

$$\begin{aligned} ER(t) &= ER(0)\ \exp\ (-k\ t) + ER_{eq}[1-\exp(-k\ t)] \\ &= ER(0) + \left[ER_{eq} - ER(0)\right]\left[1-\exp(-k\ t)\right] \end{aligned}$$

ER(t) is taken to be a weighted average of initial and equilibrium values, with weight on the latter increasing over time (but at a slowing rate). Thus ER transitions smoothly from ER(0) toward its new equilibrium. Setting ER_{eq} = 0 recovers the exponential decay of the former smoker's ER. ER(t) can also increase: for example, for a newly initiated smoker ER(0) = 0 and ER(t) increases toward ER_{eq}. Both this gradual rise of ER after initiation and its subsequent decay after quitting are illustrated in Figure 3 (black curve on lower plot), further explained below.

Conveniently, the equation still applies if time t is redefined as relative to the current time in the simulation, so that the initial value ER(0) is the current value. Thus, if a simulation steps through time in 1-year intervals and k is in per-year units, ER(t) can be updated annually simply by setting t = 1 in the equation above.

The parameters k and ER_{eq} are not necessarily constant, and this annual update makes it straightforward to vary both k and ER_{eq} over time, by simply using current values of k and ER_{eq} for each simulated individual as the simulation steps through each calendar year. We incorporated the slowing of ER decay rates k with age in Figure 2 this way, and also changed ER_{eq} with product use changes as illustrated in Figure 3. Note that the ER_{eq} profile follows the shape of the CPD profile in Figure 3, but the smoker's 50% CPD reduction at age 35 results in a much smaller reduction in ER_{eq} (due to the shape of the CPD-RR fit in Figure 1), which in turn results in a very small ER reduction. After the smoker quits at the age of 40, the ER decays gradually toward zero. However, the death rate (gray line) still generally increases with age, since death rates do so even for never-smokers (dotted line).

To project cumulative deaths in a population in various scenarios, a Monte Carlo simulation model was developed. This generates random individual tobacco use histories, with gradual ER transitions as described. An initial population of US adults, characterized by age, sex, and smoking status, is specified in the initial year, 2012, and then is updated yearly throughout the forecast period to 2060. For each simulated individual, the initial smoking status is set to current smoker, former smoker with a specified number of years since quitting, or never-smoker. Current and former smokers are assigned a single CPD over their smoking period, representing an average over this period (not just on days when cigarettes are smoked). This CPD varies from <1 to 36, based on random draws of proportions of smokers in six categories. Only adult (at least 18 years old) tobacco use is simulated. The simulation was calibrated with demographic datasets from the US Census Bureau and with cigarette use data

from National Survey on Drug Use and Health (NSDUH) for the period 2002 to 2009, reserving 2010–2012 data for model validation, except that CPD data used year 2012 as the most relevant year. Fits to smoking prevalence data in both periods were reasonably accurate (see Online Supplement for additional detail).

Each year, the model increments ages, updates smoking statuses, adds incoming new 18-year-olds, and records deaths, using input rates of initiation, cessation, and death as a function of age and sex. Each smoker death rate is the corresponding never-smoker death rate multiplied by a smoker RR. This RR is the equilibrium smoker RR adjusted (in terms of ER) for time since initiation as described. In addition, the RR is adjusted for the smoker's CPD with a multiplier. This multiplier is the ratio of the fitted, logarithmic ER function shown in Figure 1 to the average ER across all smokers (by sex). Each former smoker death rate accounts for CPD the same way, but with exponential decay of their previous CPD-adjusted ER before quitting.

A hypothetical second product (MRTP), which could be an e-cig or a similar product with reduced risk, is introduced after the first year. A proportion of the new adult population initiates the MRTP instead of conventional cigarettes, and an additional proportion of the new population that would not have initiated conventional cigarettes also initiates the MRTP. In addition, a small proportion of former smokers takes up the MRTP. Conventional cigarette smokers can transition to and from dual use of conventional cigarettes and the MRTP. Dual users can then transition to and from being exclusive MRTP users. Direct switching is omitted for simplicity. Dual users reduce their CPD by a specified percentage and also are given a slightly higher cigarette quit rate, while incurring an additional ER from the second product. Each of these transitions results in an update to ER_{eq}, and therefore to $ER(t)$ and the probability of subsequent transition to death. A model diagram showing the subpopulations and possible transitions is included in the Online Supplement.

The MRTP input values assumed for the illustrative two-product reference scenario in Figure 4 are:

1. Initiation: 25% of would-be conventional cigarette initiators instead initiate the MRTP; an additional 5% (in the same units)

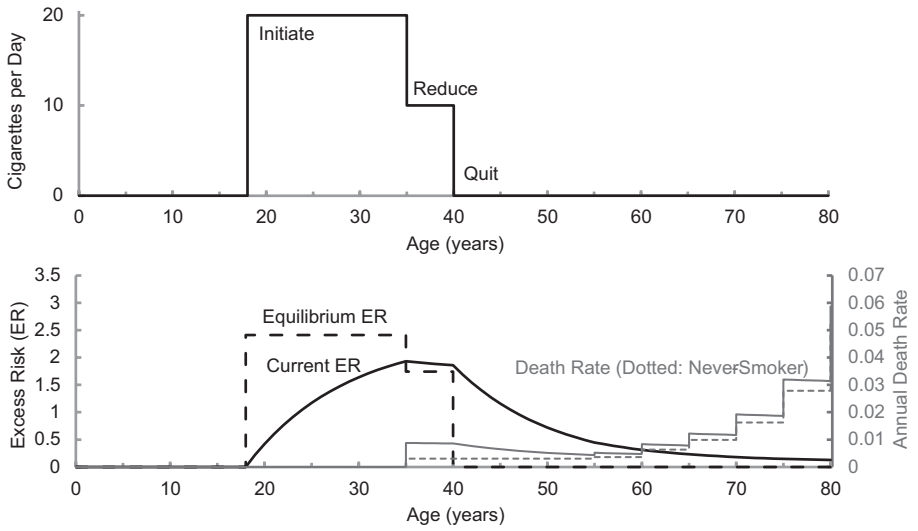

Figure 3. Example individual smoking history and risks. Top: a smoker initiates smoking at age 18, reduces cigarettes per day (CPD) by half at age 35, and quits at age 40. Bottom: Excess Risk (ER) rises or falls gradually after each change toward the equilibrium ER.

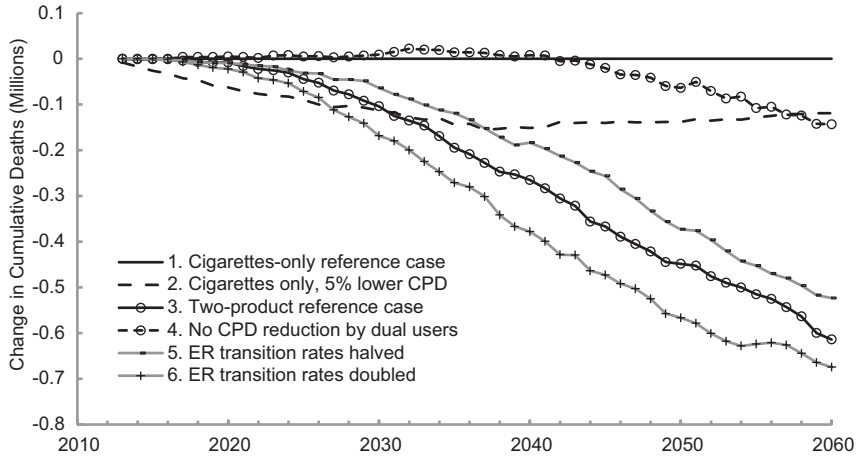

Figure 4. Sensitivity of illustrative simulated cumulative US deaths to cigarettes per day (CPD) reduction and to Excess Risk transition rates. See text for scenario descriptions.

who would have been non-users without the MRTP instead initiate the MRTP; former smokers take up the MRTP at 0.5% per year.
2. Dual use: smokers add the MRTP at 5% per year; MRTP users add conventional cigarettes at 0.5% per year.
3. CPD and mortality: dual users smoke 42% fewer CPD, reducing ER by a smaller percentage depending on initial CPD, typically by 25%.
4. Quitting: MRTP users quit at the same rate as smokers (age and sex dependent); dual users quit the MRTP (reverting to conventional cigarettes) at 0.5% per year and quit conventional cigarettes (switching completely to the MRTP) at 125% of the smoker quit rate.
5. Health risk: the ER of mortality from the MRTP relative to no tobacco use is 4% of that of conventional cigarette smoking. Risks for each dual user are summed, that is, 104% of that of the same person as a conventional cigarette smoker only.

A large sample size is needed to accurately capture subgroup demographic changes over time, as only a small proportion of the population uses any tobacco products. The simulations in Figure 4 each sampled 500 000 individuals. The model is implemented in Microsoft Excel with the individual simulations calculated within Excel's Visual Basic for Applications. While the model could be ported to other platforms, Excel provides a familiar user interface and plotting capabilities and has been used in other tobacco simulation models such as David Levy's *SimSmoke*.[30]

Results

The exponential ER decay curves after quitting, shown as dashed curves in Figure 2, were fitted to more complex relationships previously developed.[15] They did not differ substantially between men and women and therefore were estimated with pooled genders, as follows: ER decreases 9.5% per year at ages 40 and 50, 6.5% per year at age 60, and 4.5% per year at age 70 (and a 2.5% decrease per year at age 80 is not shown). These slopes were used not just after quitting but after initiation and CPD reduction (as illustrated in Figure 3 bottom plot), as well as transitions to and from the second tobacco product.

Six scenarios were simulated and compared in terms of cumulative deaths through year 2060 (Figure 4):

1. Conventional cigarettes-only reference scenario, without a second product. Results from this scenario were subtracted from all scenarios to express results relative to this scenario.
2. The same as Scenario 1 except that each simulated CPD was reduced by 5%, reducing mortality according to the fitted relationship in Figure 1. Results show a moderate effect.
3. Two-product reference scenario, in which the second product is introduced in the second year, 2013. Transitions are conventional cigarette or MRTP initiation, MRTP addition (with CPD reduction), and quitting. Avoided deaths increase over time as some smokers change to dual use, reducing CPD, and some then transition to MRTP use only.
4. The same as Scenario 3 except that CPD reduction by dual users is removed. Results are initially similar to Scenario 1: without CPD reduction, the additional RR of the MRTP, together with relapse of former smokers to the MRTP, offsets the favorable effects of the assumed higher conventional cigarette quit rates among dual users and lower RR of MRTP-only users. In later years, the latter effects accumulate as the young population when the MRTP was introduced reaches higher-mortality ages, and results become similar to Scenario 2.
5. The same as Scenario 3 except that all ER transition rates are halved, slowing transitions toward the new equilibrium after each change in tobacco use (stretching out the "current ER" curve of Figure 3). Avoided deaths decrease moderately.
6. The same as Scenario 3 except that all ER transition rates are doubled, speeding transitions. Avoided deaths increase moderately.

Discussion

We extended and implemented methods proposed for changes in RR following changes in tobacco exposure.[28] Exponential decay of ER after quitting was extended to exponential change between any two equilibrium ER levels, such as ER before and after smoking reduction, or before and after initiating a tobacco product. The exponential slopes (the slopes of the logarithm of ER(t)), were allowed to become less steep with age, implying that the ER associated with smoking decays after quitting more slowly at older ages. We also accounted for the effect of CPD on RR with a concave (logarithmic) function fitted to CPD-ER data, rather than assuming proportional or convex dose–response functions as done previously.[28]

Then we used a Monte Carlo simulation model of tobacco use in a US population to test the impact of gradual ER transitions, resulting from conventional cigarette or MRTP initiation, MRTP addition with CPD reduction, or quitting. Cumulative deaths over a long time period were compared with and without the MRTP. Though hypothetical, the selected inputs characterizing the MRTP illustrated that CPD reduction could have a substantial mortality effect. Therefore modeling of CPD reduction is important, despite evidence that quitting even from a low CPD level may reduce mortality more than just reducing CPD (eg, in Figure 1, quitting from 5 CPD reduces RR or ER by about 1, whereas reducing CPD from 10 to 5 reduces RR or ER by only about 0.5). ER transition rates also showed a substantial impact and should not be assumed to change instantly, for example after initiating a tobacco product.

In the example, availability of the MRTP reduces deaths through 2060 despite the increase in RR for dual users. This is due to the reduced CPD and increased cigarette quit rate assumed for dual users, together with the lower mortality risk for MRTP-only users. If dual users do not reduce CPD, the MRTP still reduces deaths through 2060 to a lesser extent (0.14 million). By 2060, this effect is similar to an immediate 5% CPD reduction without the MRTP. For comparison, without the MRTP a 10% increase in cigarette cessation rates, or a 10% decrease in cigarette initiation rates, would reduce deaths through 2060 by 0.22 million or 0.08 million respectively (results are not shown; note that initiation rate changes take much longer to affect deaths than cessation rate changes). Thus, CPD reduction, however achieved, could show effects similar to policies that increase cessation or reduce initiation.

The individual Monte Carlo simulation approach used here made it straightforward to capture impacts of CPD reduction and gradual ER changes This is an advantage over more commonly used Markov state models of population dynamics, where every possible state of an individual, including CPD and ER levels, would need to be enumerated. Despite the need to simulate a very large sample in order to achieve stable results, the Monte Carlo approach provides valuable modeling flexibility. Each individual's full tobacco use

history is available for the RR calculations described and for future, more sophisticated calculations.

Limitations and Future Directions

A key limitation is limited data and consequent limited understanding regarding how ER changes with time after a change in tobacco exposure (as well as with age and sex), beyond previous modeling of ER after quitting.[15] The age-dependent transition rates after quitting were applied to all ER transitions, an assumption for simplicity that should be reviewed. However, this seems more reasonable than instant transition, which would for example remove any distinction between ER (both while smoking and after quitting) for a short-term versus long-term smoker.

Another limitation is that the cigarette smoking projections are uncertain and are intended to represent a US population with low and declining smoking prevalence, so may not apply to countries with higher smoking prevalence. Moreover, assumptions for the hypothetical second product are illustrative and may not apply to future MRTP candidates. Longer-term studies of patterns of uptake of, and quitting from, e-cigs and other potential MRTPs are needed, though complicated by the rapid evolution of product characteristics, popularity, and regulation. In particular, better understanding is needed of patterns and durability of CPD reduction by dual users; if for example dual users eventually revert toward former CPD levels, as some studies have suggested,[31] CPD reduction may provide little benefit. On the other hand, a substantial benefit from smoking reduction, widely recognized, could provide smokers extra incentive to reduce as a meaningful step toward quitting.

Supplementary Material

Supplementary data are available at *Nicotine & Tobacco Research* online.

Funding

This work was funded by JT International SA through a contract with Certara.

Declaration of Interests

BP is a paid consultant to, and FT is employed by, JT International SA, which covered all costs of this analysis. JT International SA other than FT had no role in the design, conduct, or interpretation of the analysis or content of the manuscript. The views expressed are solely those of the authors and do not necessarily represent those of JT International SA.

Acknowledgments

The advice of the peer reviewers is gratefully acknowledged.

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