

An Assessment of the Cox Proportional Hazards Regression Model for Epidemiologic Studies

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The basic assumptions of the Cox proportional hazards regression model are rarely questioned. This study addresses whether hazard ratio, i.e., relative risk (RR), estimates using the Cox model are biased when these assumptions are violated. We investigated also the dependence of RR estimates on temporal exposure characteristics, and how inadequate control for a strong, time-dependent confounder affects RRs for a modest, correlated risk factor. In a realistic cohort of 500,000 adults constructed using the National Cancer Institute Smoking History Generator, we used the Cox model with increasing control of smoking to examine the impact on RRs for smoking and a correlated covariate X. The smoking-associated RR was strongly modified by age. Pack-years of smoking did not sufficiently control for its effects; simultaneous control for effect modification by age and time-dependent cumulative exposure, exposure duration, and time since cessation improved model fit. Even then, residual confounding was evident in RR estimates for covariate X, for which spurious RRs ranged from 0.980 to 1.017 per unit increase. Use of the Cox model to control for a time-dependent strong risk factor yields unreliable RR estimates unless detailed, time-varying information is incorporated in analyses. Notwithstanding, residual confounding may bias estimated RRs for a modest risk factor.

KEY WORDS: Bias (epidemiology); confounding factors (epidemiology); cox proportional hazards models; mortality; smoking

1. INTRODUCTION

The proportional hazards (PH) model, originally proposed by Cox⁽¹⁾ for the analysis of data from clinical trials, was soon adopted by epidemiologists and today provides the conceptual framework for analyses of both cohort and case-control studies. The clinical trial populations for which the Cox model was originally used had fixed and uniform exposures, a

short duration of follow-up, and an absence of confounding because these were randomized studies. By contrast, applications of the Cox model to observational epidemiology frequently involve heterogeneous and time-varying exposures, many years of follow-up, and confounding by numerous measured and unmeasured risk factors.

While the PH framework has been highly successful in identifying and quantifying major risk factors for human disease, this method is now increasingly being applied to exposures that confer smaller risks. This application prompts questions about whether some of the fundamental assumptions underlying the use of the PH model, which can reasonably be expected to hold for the generally short time frames of clinical trials, can also be expected to hold over the much longer time frames typical of epidemiologic studies, and how violation of these assumptions might impact results. Another concern is

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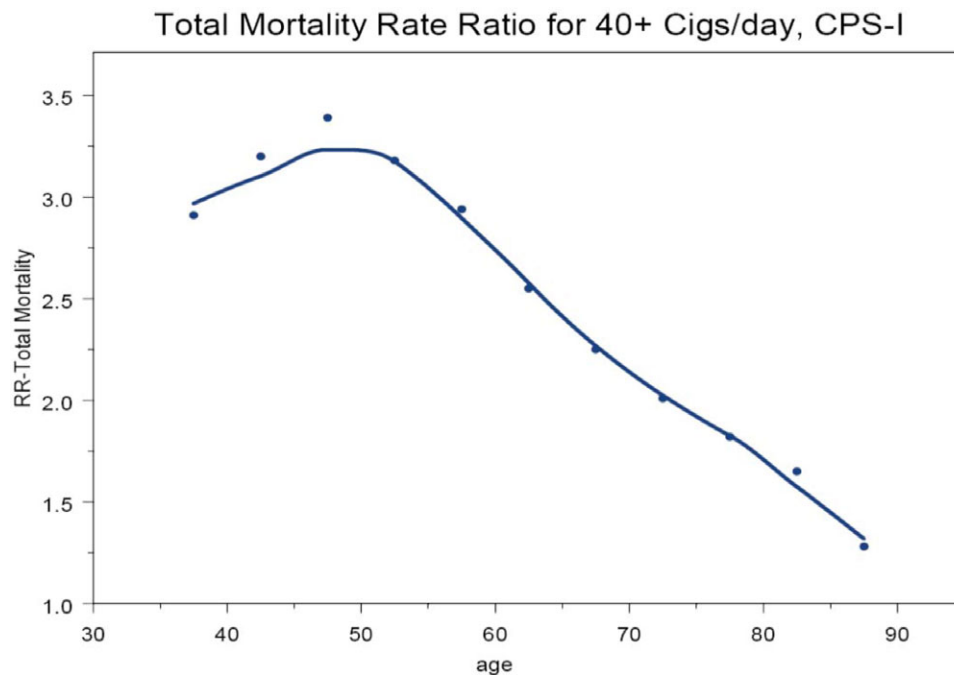


Fig. 1. Rate ratios for all-cause mortality among smokers of two packs of cigarettes per day, compared with nonsmokers, from the American Cancer Society Cancer Prevention Study I (CPS-I) cohort.⁽²⁾ The line is a statistical smoother through the rate ratios. This figure illustrates dramatically how poor the assumption of proportionality of hazards is for smoking-associated risks. If proportionality of hazards held, the rate ratios should lie on a horizontal line.

that observational exposure histories are often much more complex than those considered in clinical trials.

The main assumption of the original PH model is that the hazard ratio remains constant with time. With age as the time axis, as is common in epidemiologic studies, this assumption stipulates no effect modification by age. The failure of this assumption can be seen in a plot of age-specific rate ratios for all-cause mortality among heavy smokers, where strong effect modification of smoking intensity by age is apparent (Fig. 1).⁽²⁾ Moreover, the rate ratios after age 50 unexpectedly decrease with increasing cumulative smoking exposure, as mortality rates among never smokers rise rapidly with age. This example demonstrates that for both intensity of exposure and cumulative exposure, which are commonly used measures of exposure, the hazard ratio does not remain constant along the primary time axis. In fact, there is accumulating evidence that the entire pattern of exposure to a risk factor, such as cigarette smoking, is important in determining risk, and that no single measure of exposure can capture the impact of such a risk factor on disease incidence.^(3–10)

Another related, but perhaps more fundamental, issue is the focus on the hazard ratio (henceforth referred to as relative risk, RR) as the target of estima-

tion in the PH model. The lack of a requirement for estimation of a background hazard function is widely viewed as a desirable property of this model. However, direct estimation of hazard functions instead of the RR, particularly with cohort data, would allow consideration of other measures of risk, such as attributable risk (i.e., the difference in absolute hazards for varying levels of exposure). Furthermore, direct parametric estimation of hazards as functions of exposure allows flexible modeling of temporal aspects of exposure and risk, as discussed below and in papers describing the use of parametric models for analyses of data in cancer epidemiology.⁽¹¹⁾

These observations raise at least two fundamental questions. First, how does the use of the PH model impact estimates of the health effect of a strong risk factor, such as cigarette smoking, when that effect varies over the time scale and depends also on temporal factors in exposure, such as age at start, intensity, duration, age at cessation, and time since cessation? When temporal factors in exposure are important in determining risk, an estimate of risk based on a summary measure of exposure, such as cumulative exposure (pack-years of smoking, for example), may yield misleading information on the true impact of the exposure on risk. Second, if this

model does not allow adequate control of a strong risk factor, such as cigarette smoking, how does this lack of adequate control affect the RR estimates for much more modest putative risk factors, such as air pollution, whether or not they are correlated with cigarette smoking?

While the PH model has been extended to accommodate time-varying covariates and flexible exposure-response relationships for the RR, often only summary measures of exposure are available in epidemiologic studies. The questions raised above are then particularly relevant because analyses of these data can be based only on the available measures of exposure, which could lead to misleading conclusions regarding the impact of those exposures on risk. As is discussed below, the use of the PH model also places implausible constraints on how temporal factors, such as duration of exposure, are used in analyses.

To address these questions, the direct approach would be to analyze a cohort data set in which detailed time-varying smoking and all-cause mortality information is available on an individual level. With such a data set, one could use the PH model to analyze the data using various measures of exposure to investigate how estimates of risk change with increasingly detailed specification of exposure. One could also examine how the impact of a modest risk factor, such as air pollution, is affected by the way smoking exposures are modeled. In the absence of access to such a data set, an alternative approach is to generate simulated cohort data sets that provide a realistic depiction of smoking-associated all-cause mortality. A simulated covariate with varying degrees of correlation with smoking, but no impact on mortality (i.e., an estimated effect of zero if smoking is adequately controlled), can then be introduced to investigate how the extent of control for smoking affects the observed association of the covariate with mortality. Taking the latter approach, we implemented the U.S. National Cancer Institute (NCI)'s Smoking History Generator (SHG) to generate life histories in a simulated cohort of 500,000 men and women, and then used this cohort to conduct the various analyses contemplated above.

2. METHODS

2.1. Smoking History Generator

The SHG was developed by the Cancer Intervention and Surveillance Modeling Network (CISNET)

lung cancer program as part of a joint effort between the NCI and various universities and research centers in the United States and Europe. Following the U.S. Surgeon General's first report on smoking and health,⁽¹²⁾ the original SHG⁽¹³⁾ was developed by the NCI-sponsored CISNET consortium to investigate the impact of changes in smoking behavior on lung cancer⁽⁷⁾ between 1975 and 2000 in the United States and all-cause mortality⁽¹⁴⁾ between 1964 and 2012. The SHG is a stochastic simulation that begins at birth and follows each individual through life while simulating smoking behaviors, including current smoking status, age at initiation, number of cigarettes smoked per day, and age at any changes in smoking habits, including cessation.

The SHG that we used addressed deaths from all causes other than lung cancer. The SHG was first developed to estimate the impact of changing tobacco smoking behavior on lung cancer mortality in the United States between 1975 and 2000. One element of this effort required adjustment for mortality due to causes other than lung cancer so that lung cancer risks could be accurately estimated. This is the reason that this SHG simulates other-cause mortality rather than all-cause mortality. Because lung cancer deaths comprise only a small fraction of all deaths, life tables for all-cause mortality minus lung cancer are close approximations to life tables for all-cause mortality. Therefore, for simplicity, we refer to results hereafter as being for "all-cause mortality" rather than "all-cause mortality excluding lung cancer."

Data incorporated into the SHG are derived from the National Health Interview Surveys from 1965 to 2009, the National Center for Health Statistics, the Human Mortality Database, and American Cancer Society Cancer Prevention Studies (CPS) I and II.^(14,15) By capturing information on changing smoking initiation and cessation rates over time and by birth cohort, the SHG offers a realistic approach to simulation of individual life histories in smoking populations. Further information on the SHG can be found in recent publications.^(7,16)

2.2. Simulated Cohort

Cohort studies of air pollution and all-cause mortality are quintessential examples of studies that must control for a potentially strong confounder (smoking) to investigate the impact of a much more modest risk factor. One of the most important and influential studies in this area is based on CPS-II, a prospective cohort mortality study of approximately

1.2 million U.S. men and women aged ≥ 30 years in 1982.⁽¹⁷⁾ By linkage to ecologic (i.e., area-level) air pollution data from centrally located monitors, Pope *et al.*⁽¹⁸⁾ conducted an analysis of associations between particulate matter (PM) and mortality among 552,138 CPS-II cohort members who resided at baseline in metropolitan areas within the 48 contiguous U.S. states, had completed questionnaire data on risk factors evaluated, and had available death certificates if deceased.

To mimic the structure of the CPS-II cohort, we randomly selected 500,000 men and women aged 30–70 years, the range of ages at entry in the Pope *et al.* study,⁽¹⁸⁾ from a generated pool of 2 million individuals constructed to match the age and sex distribution of the 1980 U.S. population according to the national census. In two prominent papers, Pope *et al.*^(18,19) followed mortality in this population to 1998. The SHG allowed us to follow mortality in the simulated cohort to 2000. The smoking history and death of each cohort member were generated using the SHG. Supplemental Tables I through IV show typical life tables over the period 1980 through 2000 for cohorts generated in this manner, stratified by smoking history.

As described in the Supplemental Materials, we generated a covariate X that was correlated with smoking but had no impact on mortality.

2.3. Statistical Analysis

We first examined survival curves by smoking status, as described in Doll *et al.*,^(20,21) to determine how well our simulated data set described mortality by smoking status in a real data set. As an additional check, we compared our mortality data by smoking status with those developed by Woloshin *et al.*⁽²²⁾ based on U.S. national death and smoking prevalence data and mortality RRs by smoking status from the CPS-II cohort. To generate survival curves from the mortality rates calculated by Woloshin *et al.*,⁽²²⁾ we generated 100,000 hypothetical persons aged 35 years for each category of sex and smoking. At each year of age up to 84 years, a person was subject to the risk of death reported by Woloshin *et al.*⁽²²⁾ Survival was then estimated using the conventional Kaplan–Meier method.

Second, we used the Cox PH model with increasingly sophisticated control of smoking to investigate how better control of smoking impacts both the estimates of smoking-associated RRs and those associated with the correlated covariate X. We

classified smoking in several ways, for example, according to never, former, or current smoking status as of 1980, or according to never/former/current smoking status plus duration of smoking and packs of cigarettes smoked per year, or based on duration, packs smoked, and time since smoking cessation. The latter approach is the same as that used in many epidemiologic cohorts, including the Pope *et al.* analysis of CPS-II.⁽¹⁸⁾ We also explored incorporation of smoking as a time-varying covariate, an approach that cannot be used in cohorts that do not collect detailed longitudinal information on smoking behaviors over time. We then estimated associations between covariate X and all-cause mortality using Cox PH regression models, with baseline hazards stratified by age in 1980 and sex. To provide progressively better control for cigarette smoking, we also used time-dependent Cox models with interaction terms to accommodate modification of the smoking effect by age, i.e., nonproportionality of the smoking RR.

3. RESULTS

The age distribution of the simulated cohort by calendar year is shown in Fig. 2. To ensure that the simulated life tables were a reasonable representation of overall survival statistics in the United States, we confirmed that age- and sex-specific death rates in the cohort between 1980 and 2000 corresponded closely with U.S. national death rates from the Social Security Administration⁽²³⁾ and the Human Mortality Database⁽²⁴⁾ (see Supplemental Figs. 1a through 1E).

To evaluate whether the mortality experience within each smoking stratum was a reasonable representation of reality, we compared smoking-related survival curves with those from the British doctors' study cohort.^(20,21) Age-specific survival curves by smoking status and birth cohort in the simulated data set (see Supplemental Figs. 2a through 2d for survival from age 35 years; Supplemental Figs. 3a and 3b for survival from age 60 years) had shapes that resembled those from the British doctors' study cohort, confirming that our simulated life histories were a reasonable representation of life histories in smoking populations. We also demonstrated that the smoking-stratified survival curves in the simulated cohort were similar to those based on U.S. national mortality rates by age, sex, and smoking status, as calculated by Woloshin *et al.*⁽²²⁾ (see Supplemental Figs. 4a and 4b).

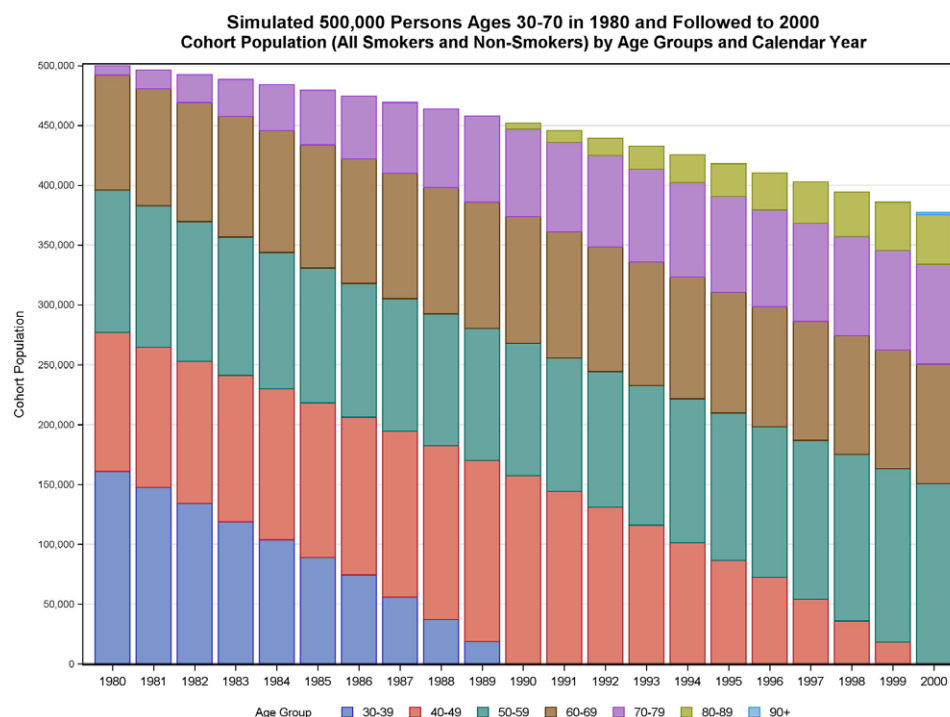


Fig. 2. Age distribution of the simulated cohort of 500,000 men and women aged 30–70 years by calendar year from 1980 to 2000. This age distribution is designed to match that of the U.S. adult population (within the defined age range) in 1980 according to the national census.

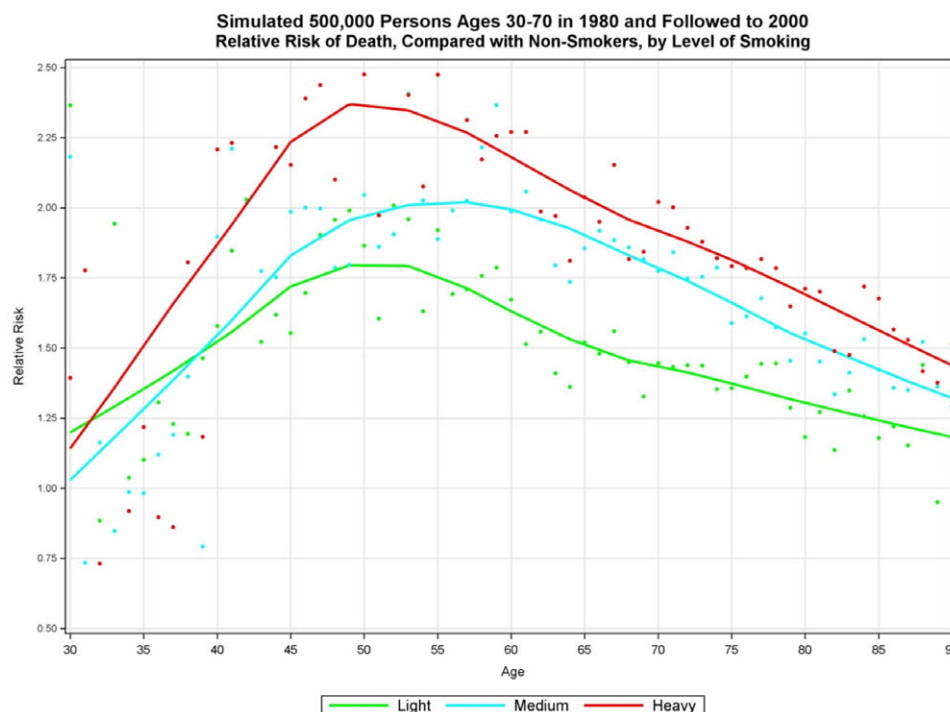


Fig. 3. Age-specific relative risk of death from all causes among light, medium, and heavy smokers compared with nonsmokers in a simulated cohort of 500,000 men and women. Note the effect modification of the relative risk by age, a pattern similar to that found in the American Cancer Society Cancer Prevention Study I (shown in Fig. 1).

In addition to generating individual-level smoking histories, the SHG classifies smokers as light, medium, or heavy. Based on the simulated life table, we examined the mortality RRs for these three classes of smokers (Fig. 3). This figure shows the same pattern of strong effect modification by age as was seen in CPS-I (Fig. 1) and further confirms that the mortality experience and impact of smoking in the simulated cohort were as expected based on the epidemiological literature.^(2,20,21)

Tables I and II show the results of Cox PH regression models with progressively increasing control for smoking, with and without covariate X. Starting with the crudest control of smoking (current, former, and never), we considered more detailed models including, ultimately, time-dependent control allowing for effect modification by age. Specifically, we considered the following series of models: 1) current smokers, former smokers, and never smokers; 2) in addition to model 1, number of packs smoked for current and former smokers; 3) in addition to model 2, duration of smoking for current and former smokers; 4) total packs smoked, duration of smoking for current and former smokers, and time since cessation for former smokers.

Time-independent and time-dependent versions of each model were run with various levels of correlation with the covariate X (Pearson $\rho = -0.9$ to $+0.9$; data shown only for $|\rho| = 0.0, 0.1, 0.5$, and 0.9). Table II shows the results of fitting the most elaborate model for control of smoking, using the time-dependent versions of the covariates in model 4 together with interaction between pack-years and attained age using a cubic polynomial. In Supplemental Table V, a cubic polynomial is used to model the interaction between the covariate X and attained age (in addition to all of the covariates in the model presented in Table II).

Compared with models that included only smoking variables, adding covariate X and strengthening the correlation between smoking and covariate X decreased the Akaike information criterion (AIC), even though covariate X was not independently associated with mortality (Table I; Fig. 5). The improvement in AIC indicates inadequate adjustment for smoking, such that including correlated covariate X adjusted the biased impact of smoking estimated using the PH model. Fig. 5 shows the RRs and 95% CIs associated with covariate X. Each panel of that figure depicts the RRs for a specific correlation between X and smoking and five distinct models for control of smoking. In each panel, models 1

through 5 implement increasingly elaborate control of smoking. Moving across each panel from model 1 to model 5, the AIC generally indicates an improvement in model fit (i.e., the AIC decreases), with one exception: the AIC for model 4 is higher than the AIC for model 3. Model 3 incorporates duration of smoking, whereas model 4 incorporates both duration of smoking and time since quitting. Thus, although time since quitting is known to be an important determinant of the risk associated with smoking, incorporating it into the PH model in a linear fashion does not improve model fit. Model 5 includes duration of smoking and time since quitting, and also allows for effect modification by age. For each correlation, model 5 fits the data considerably better than models that do not allow for effect modification by age.

Although covariate X is not a confounder because it is not associated with mortality, in these analyses it appears to be a confounder because smoking is inadequately controlled in even the most detailed models used. Any divergence from an RR of 1 for covariate X represents the impact of “residual confounding” due to inadequate control for smoking. When smoking was classified crudely based on smoking status, a stronger positive correlation between smoking and covariate X resulted in stronger positive confounding of the association between covariate X and mortality. The RR for covariate X reached a maximum of 1.017 with $\rho = +0.9$ and smoking status coded as a time-independent variable. Little difference was seen with smoking status coded as a time-dependent variable (maximum RR = 1.017 with $\rho = +0.9$) (Table I; Fig. 5). Conversely, a stronger negative correlation between smoking and covariate X resulted in stronger negative confounding of the association between covariate X and mortality, with the RR reaching a minimum of 0.980 with $\rho = -0.9$ and time-independent smoking status. Fig. 5 shows the RRs for different correlations and time-dependent smoking models.

By contrast, when smoking was classified based on smoking status and total packs smoked, with or without duration, a stronger positive or negative correlation with covariate X resulted in stronger negative confounding, albeit of lower magnitude than with adjustment only for smoking status (Table I). After adjusting for smoking status, packs, and duration (as in CPS-II), RRs for covariate X were as low as 0.992 and 0.989 with $\rho = +0.9$ in time-independent and time-dependent covariate models, respectively, and 0.986 and 0.997 with $\rho = -0.9$ in

Table 1. Associations Between Covariate X and All-Cause Mortality Based on Cox Proportional Hazards Regression Analysis Controlling for Time-Independent or Time-Dependent Smoking (Coded as Status Only or Status, Packs, and Duration) with Baseline Hazards Stratified by Age and Sex in a Simulated Cohort of 500,000 Men and Women; Correlation Shown is the Pearson Correlation Coefficient Between Packs Smoked and Covariate X

Correlation	AIC with Covariates (Time-Independent; Time-Dependent)	Covariate Description	Time-Independent Smoking Variables		Time-Dependent Smoking Variables		
			RR	95% CI	RR	95% CI	
Model Covariates: Smoking Status							
N/A	2576580.7;	Current vs. Nonsmoker	1.759	(1.736 – 1.783)	1.769	(1.746 – 1.793)	
	2546781.2	Former vs. Nonsmoker	1.131	(1.114 – 1.148)	1.128	(1.111 – 1.145)	
Model Covariates: Smoking Status and Covariate X							
$\rho = 0.0$	2576580.5;	Current vs. Nonsmoker	1.771	(1.743 – 1.800)	1.765	(1.736 – 1.793)	
	2546782.9	Former vs. Nonsmoker	1.139	(1.119 – 1.160)	1.125	(1.105 – 1.146)	
$\rho = +0.1$	2576582.4;	Covariate X (Per Unit)	0.999	(0.998 – 1.000)	1.000	(0.999 – 1.002)	
		Current vs. Nonsmoker	1.754	(1.726 – 1.783)	1.748	(1.720 – 1.777)	
		2546777.0	Former vs. Nonsmoker	1.128	(1.108 – 1.148)	1.115	(1.095 – 1.135)
$\rho = +0.5$	2576378.8;	Covariate X (Per Unit)	1.000	(0.999 – 1.002)	1.002	(1.000 – 1.003)	
		Current vs. Nonsmoker	1.635	(1.608 – 1.663)	1.632	(1.605 – 1.660)	
		2546540.4	Former vs. Nonsmoker	1.063	(1.045 – 1.082)	1.054	(1.035 – 1.072)
$\rho = +0.9$	2575773.0;	Covariate X (Per Unit)	1.009	(1.007 – 1.010)	1.009	(1.008 – 1.011)	
		Current vs. Nonsmoker	1.535	(1.510 – 1.560)	1.541	(1.516 – 1.566)	
		2545961.9	Former vs. Nonsmoker	1.033	(1.016 – 1.050)	1.029	(1.012 – 1.046)
$\rho = -0.1$	2576541.4;	Covariate X (Per Unit)	1.017	(1.016 – 1.018)	1.017	(1.016 – 1.018)	
		Current vs. Nonsmoker	1.811	(1.782 – 1.840)	1.804	(1.776 – 1.833)	
		2546764.4	Former vs. Nonsmoker	1.167	(1.146 – 1.188)	1.152	(1.132 – 1.173)
$\rho = -0.5$	2576156.3;	Covariate X (Per Unit)	0.996	(0.995 – 0.997)	0.997	(0.996 – 0.999)	
		Current vs. Nonsmoker	1.914	(1.885 – 1.944)	1.905	(1.876 – 1.935)	
		2546461.0	Former vs. Nonsmoker	1.261	(1.238 – 1.285)	1.241	(1.218 – 1.264)
$\rho = -0.9$	2575397.6;	Covariate X (Per Unit)	0.987	(0.986 – 0.989)	0.989	(0.988 – 0.990)	
		Current vs. Nonsmoker	2.013	(1.982 – 2.044)	1.999	(1.968 – 2.030)	
		2545838.2	Former vs. Nonsmoker	1.386	(1.360 – 1.413)	1.355	(1.329 – 1.381)
		Covariate X (Per Unit)	0.980	(0.979 – 0.981)	0.982	(0.981 – 0.984)	
Model Covariates: Smoking Status and Packs							
N/A	2575420.3;	Current vs. Nonsmoker	1.479	(1.454 – 1.504)	1.441	(1.416 – 1.465)	
	2545401.4	Former vs. Nonsmoker	1.017	(1.000 – 1.034)	1.020	(1.003 – 1.036)	
		Packs Smoked (Per 365)	1.005	(1.005 – 1.006)	1.005	(1.005 – 1.005)	
Model Covariates: Smoking Status, Packs, and Covariate X							
$\rho = 0.0$	2575414.5;	Current vs. Nonsmoker	1.497	(1.469 – 1.526)	1.443	(1.416 – 1.471)	
		2545403.2	Former vs. Nonsmoker	1.030	(1.011 – 1.050)	1.022	(1.003 – 1.041)
			Packs Smoked (Per 365)	1.005	(1.005 – 1.006)	1.005	(1.005 – 1.005)
			Covariate X (Per Unit)	0.998	(0.997 – 0.999)	1.000	(0.999 – 1.001)
$\rho = +0.1$	2575403.8;	Current vs. Nonsmoker	1.505	(1.477 – 1.533)	1.454	(1.427 – 1.482)	
		2545398.0	Former vs. Nonsmoker	1.036	(1.017 – 1.055)	1.030	(1.011 – 1.049)
			Packs Smoked (Per 365)	1.005	(1.005 – 1.006)	1.005	(1.005 – 1.005)
			Covariate X (Per Unit)	0.997	(0.996 – 0.999)	0.999	(0.997 – 1.000)
$\rho = +0.5$	2575402.0;	Current vs. Nonsmoker	1.498	(1.471 – 1.524)	1.455	(1.430 – 1.482)	
		2545388.5	Former vs. Nonsmoker	1.031	(1.013 – 1.049)	1.033	(1.015 – 1.051)
			Packs Smoked (Per 365)	1.006	(1.005 – 1.006)	1.005	(1.005 – 1.006)
			Covariate X (Per Unit)	0.997	(0.995 – 0.998)	0.997	(0.996 – 0.999)
$\rho = +0.9$	2575395.9;	Current vs. Nonsmoker	1.482	(1.457 – 1.507)	1.440	(1.416 – 1.465)	
		2545343.9	Former vs. Nonsmoker	1.021	(1.004 – 1.038)	1.033	(1.016 – 1.050)
			Packs Smoked (Per 365)	1.007	(1.006 – 1.008)	1.007	(1.006 – 1.007)
			Covariate X (Per Unit)	0.993	(0.991 – 0.996)	0.991	(0.989 – 0.993)
$\rho = -0.1$	2575403.2;	Current vs. Nonsmoker	1.510	(1.482 – 1.540)	1.453	(1.425 – 1.482)	
		2545400.4	Former vs. Nonsmoker	1.040	(1.020 – 1.060)	1.029	(1.009 – 1.048)
			Packs Smoked (Per 365)	1.005	(1.005 – 1.006)	1.005	(1.005 – 1.005)
			Covariate X (Per Unit)	0.997	(0.996 – 0.999)	0.999	(0.998 – 1.000)
$\rho = -0.5$	2575391.5;	Current vs. Nonsmoker	1.540	(1.506 – 1.574)	1.450	(1.418 – 1.483)	
		2545402.6	Former vs. Nonsmoker	1.060	(1.037 – 1.084)	1.026	(1.004 – 1.049)

(Continued)

Table I (Continued)

Correlation	AIC with Covariates (Time-Independent; Time-Dependent)	Covariate Description	Time-Independent Smoking Variables		Time-Dependent Smoking Variables	
			RR	95% CI	RR	95% CI
$\rho = -0.9$	2575288.4; 2545401.7	Packs Smoked (Per 365)	1.005	(1.004 – 1.005)	1.005	(1.005 – 1.005)
		Covariate X (Per Unit)	0.996	(0.995 – 0.998)	0.999	(0.998 – 1.001)
		Current vs. Nonsmoker	1.733	(1.679 – 1.788)	1.467	(1.420 – 1.515)
		Former vs. Nonsmoker	1.201	(1.162 – 1.240)	1.038	(1.006 – 1.070)
		Packs Smoked (Per 365)	1.003	(1.002 – 1.003)	1.005	(1.004 – 1.005)
		Covariate X (Per Unit)	0.989	(0.987 – 0.991)	0.999	(0.997 – 1.001)
Model Covariates: Smoking Status, Packs, and Duration						
N/A	2575404.1; 2545349.1	Current vs. Nonsmoker	1.408	(1.369 – 1.448)	1.300	(1.258 – 1.343)
		Former vs. Nonsmoker	0.984	(0.962 – 1.006)	0.962	(0.941 – 0.984)
		Packs Smoked (Per 365)	1.005	(1.005 – 1.005)	1.005	(1.004 – 1.005)
		Years Smoked (Per Year)	1.002	(1.001 – 1.002)	1.003	(1.002 – 1.003)
Model Covariates: Smoking Status, Packs, Duration, and Covariate X						
$\rho = 0.0$	2575395.2; 2545349.7	Current vs. Nonsmoker	1.422	(1.382 – 1.464)	1.305	(1.262 – 1.348)
		Former vs. Nonsmoker	0.996	(0.973 – 1.020)	0.966	(0.944 – 0.990)
		Packs Smoked (Per 365)	1.005	(1.005 – 1.005)	1.004	(1.004 – 1.005)
		Years Smoked (Per Year)	1.002	(1.001 – 1.003)	1.003	(1.002 – 1.003)
$\rho = +0.1$	2575382.6; 2545341.1	Covariate X (Per Unit)	0.998	(0.997 – 0.999)	0.999	(0.998 – 1.000)
		Current vs. Nonsmoker	1.426	(1.386 – 1.468)	1.310	(1.268 – 1.354)
		Former vs. Nonsmoker	1.000	(0.977 – 1.024)	0.973	(0.950 – 0.996)
		Packs Smoked (Per 365)	1.005	(1.005 – 1.005)	1.005	(1.004 – 1.005)
$\rho = +0.5$	2575380.1; 2545328.2	Years Smoked (Per Year)	1.002	(1.001 – 1.003)	1.003	(1.002 – 1.004)
		Covariate X (Per Unit)	0.997	(0.996 – 0.998)	0.998	(0.997 – 0.999)
		Current vs. Nonsmoker	1.417	(1.378 – 1.458)	1.306	(1.264 – 1.349)
		Former vs. Nonsmoker	0.994	(0.972 – 1.017)	0.973	(0.951 – 0.996)
$\rho = +0.9$	2575371.5; 2545273.0	Packs Smoked (Per 365)	1.005	(1.005 – 1.006)	1.005	(1.005 – 1.005)
		Years Smoked (Per Year)	1.002	(1.001 – 1.003)	1.003	(1.002 – 1.004)
		Covariate X (Per Unit)	0.996	(0.995 – 0.998)	0.997	(0.995 – 0.998)
		Current vs. Nonsmoker	1.396	(1.357 – 1.436)	1.277	(1.235 – 1.319)
$\rho = -0.1$	2575381.9; 2545344.6	Former vs. Nonsmoker	0.981	(0.959 – 1.003)	0.967	(0.945 – 0.989)
		Packs Smoked (Per 365)	1.007	(1.006 – 1.007)	1.007	(1.006 – 1.007)
		Years Smoked (Per Year)	1.002	(1.001 – 1.003)	1.003	(1.002 – 1.004)
		Covariate X (Per Unit)	0.992	(0.989 – 0.995)	0.989	(0.987 – 0.992)
$\rho = -0.5$	2575367.2; 2545347.7	Current vs. Nonsmoker	1.432	(1.391 – 1.474)	1.311	(1.269 – 1.355)
		Former vs. Nonsmoker	1.004	(0.980 – 1.028)	0.972	(0.950 – 0.996)
		Packs Smoked (Per 365)	1.005	(1.004 – 1.005)	1.004	(1.004 – 1.005)
		Years Smoked (Per Year)	1.002	(1.001 – 1.003)	1.003	(1.002 – 1.004)
$\rho = -0.9$	2575228.9; 2545340.9	Covariate X (Per Unit)	0.997	(0.996 – 0.998)	0.998	(0.997 – 1.000)
		Current vs. Nonsmoker	1.458	(1.415 – 1.503)	1.314	(1.270 – 1.359)
		Former vs. Nonsmoker	1.024	(0.998 – 1.051)	0.973	(0.949 – 0.998)
		Packs Smoked (Per 365)	1.004	(1.004 – 1.005)	1.004	(1.004 – 1.005)
NA	2576780.2; 2545697.2	Years Smoked (Per Year)	1.002	(1.001 – 1.003)	1.003	(1.002 – 1.004)
		Covariate X (Per Unit)	0.996	(0.994 – 0.997)	0.999	(0.997 – 1.000)
		Current vs. Nonsmoker	1.626	(1.570 – 1.684)	1.346	(1.296 – 1.399)
		Former vs. Nonsmoker	1.163	(1.125 – 1.203)	1.000	(0.968 – 1.032)
Model Covariates: Smoking Packs, Time Since Cessation, and Duration						
$\rho = 0.0$	2576782.2; 2545692.6	Packs Smoked (Per 365)	1.002	(1.001 – 1.002)	1.004	(1.003 – 1.004)
		Years Smoked (Per Year)	1.003	(1.002 – 1.004)	1.003	(1.002 – 1.004)
		Covariate X (Per Unit)	0.986	(0.984 – 0.988)	0.997	(0.995 – 0.999)
		Years Since Cessation (Per Year)	0.991	(0.990 – 0.991)	0.993	(0.993 – 0.994)
Model Covariates: Smoking Packs, Time Since Cessation, Duration, and Covariate X						
$\rho = 0.0$	2576782.2; 2545692.6	Packs Smoked (Per 365)	1.005	(1.004 – 1.005)	1.004	(1.004 – 1.005)
		Years Since Cessation (Per Year)	0.991	(0.990 – 0.991)	0.993	(0.992 – 0.993)

(Continued)

Table I (Continued)

Correlation	AIC with Covariates (Time-Independent; Time-Dependent)	Covariate Description	Time-Independent Smoking Variables		Time-Dependent Smoking Variables	
			RR	95% CI	RR	95% CI
$\rho = +0.1$	2576777.9; 2545699.2	Years Smoked (Per Year)	1.008	(1.008 – 1.009)	1.007	(1.007 – 1.008)
		Covariate X (Per Unit)	1.000	(0.999 – 1.001)	1.002	(1.000 – 1.003)
		Packs Smoked (Per 365)	1.005	(1.004 – 1.005)	1.004	(1.004 – 1.005)
		Years Since Cessation (Per Year)	0.991	(0.990 – 0.992)	0.993	(0.993 – 0.994)
$\rho = +0.5$	2576764.4; 2545685.6	Years Smoked (Per Year)	1.009	(1.008 – 1.009)	1.008	(1.007 – 1.008)
		Covariate X (Per Unit)	0.999	(0.997 – 1.000)	1.000	(0.999 – 1.001)
		Packs Smoked (Per 365)	1.005	(1.005 – 1.005)	1.005	(1.004 – 1.005)
		Years Since Cessation (Per Year)	0.991	(0.990 – 0.992)	0.993	(0.993 – 0.994)
$\rho = +0.9$	2576706.2; 2545568.1	Years Smoked (Per Year)	1.009	(1.008 – 1.009)	1.008	(1.007 – 1.008)
		Covariate X (Per Unit)	0.997	(0.996 – 0.998)	0.997	(0.996 – 0.999)
		Packs Smoked (Per 365)	1.007	(1.007 – 1.008)	1.007	(1.006 – 1.008)
		Years Since Cessation (Per Year)	0.991	(0.990 – 0.992)	0.994	(0.993 – 0.994)
$\rho = -0.1$	2576780.9; 2545696.6	Years Smoked (Per Year)	1.009	(1.008 – 1.009)	1.008	(1.007 – 1.008)
		Covariate X (Per Unit)	0.988	(0.986 – 0.991)	0.986	(0.984 – 0.989)
		Packs Smoked (Per 365)	1.005	(1.004 – 1.005)	1.004	(1.004 – 1.005)
		Years Since Cessation (Per Year)	0.991	(0.990 – 0.992)	0.993	(0.992 – 0.994)
$\rho = -0.5$	2576782.2; 2545672.9	Years Smoked (Per Year)	1.009	(1.008 – 1.009)	1.007	(1.007 – 1.008)
		Covariate X (Per Unit)	0.999	(0.998 – 1.001)	1.001	(1.000 – 1.002)
		Packs Smoked (Per 365)	1.005	(1.004 – 1.005)	1.005	(1.004 – 1.005)
		Years Since Cessation (Per Year)	0.991	(0.990 – 0.991)	0.992	(0.992 – 0.993)
$\rho = -0.9$	2576781.2; 2545598.6	Years Smoked (Per Year)	1.008	(1.008 – 1.009)	1.007	(1.006 – 1.007)
		Covariate X (Per Unit)	1.000	(0.999 – 1.001)	1.004	(1.002 – 1.005)
		Packs Smoked (Per 365)	1.004	(1.004 – 1.005)	1.006	(1.006 – 1.007)
		Years Since Cessation (Per Year)	0.991	(0.990 – 0.992)	0.991	(0.990 – 0.991)
		Years Smoked (Per Year)	1.009	(1.008 – 1.010)	1.005	(1.004 – 1.005)
		Covariate X (Per Unit)	0.999	(0.997 – 1.001)	1.010	(1.008 – 1.012)

AIC = Akaike information criterion; CI = confidence interval; NA = not applicable; RR = relative risk (hazard ratio).

time-independent and time-dependent models, respectively. The inverse associations with covariate X indicate that associations with smoking were overestimated in these models, and that including covariate X accounted for the overestimation by indicating a negative association, i.e., a protective effect.

Classification of smoking based on packs smoked, time since cessation, and duration of smoking resulted in progressively stronger inverse associations with covariate X in concert with a stronger positive correlation with smoking (lowest RRs = 0.988 and 0.986 in time-independent and time-dependent models, respectively, with $\rho = +0.9$), and progressively stronger positive associations when the correlation was negative, but only in

the time-dependent model (highest RR = 1.010 with $\rho = -0.9$) (Table I).

In previous analyses, temporal factors such as duration of smoking and time since cessation have been shown to be important determinants of risk for lung cancer^(5,25–28) and all-cause mortality.^(20,21) Therefore, we used models that included time-varying packs smoked, duration of smoking, time since cessation, both without and with interaction terms (to test for effect modification by age) between attained age (coded as age, age squared, and age cubed) and packs smoked. With the interaction terms, the RR of mortality per 10 pack-years of smoking showed strong effect modification by attained age (Fig. 4). The shape of the RR curve for smoking did not vary substantially with the degree

Table II. Results from Cox Proportional Hazards Regression Models for All-Cause Mortality Including Time-Dependent Smoking (Packs Smoked, Duration of Smoking, and Time Since Cessation), Covariate X, and Interactions of Attained Age (Age, Age Squared, and Age Cubed) with Packs Smoked, with Baseline Hazards Stratified by Age and Sex in a Simulated Cohort of 500,000 Men and Women; Correlation Shown is the Pearson Correlation Coefficient Between Packs Smoked and Covariate X

Correlation	AIC with Covariates	Covariate	Parameter Estimate	Standard Error	p-Value	RR	95% CI
$\rho = 0.0$	2542084.9	Smoking Packs	-0.0001236	0.0000438	0.0048		
		Smoking Duration	0.00757	0.0002163	<0.0001	1.008	(1.007 – 1.008)
		Years Since Cessation	-0.00637	0.0002747	<0.0001	0.994	(0.993 – 0.994)
		Smoking Packs \times Age	8.585E-06	2.065E-06	<0.0001		
		Smoking Packs \times Age ²	-1.528E-07	3.192E-08	<0.0001		
		Smoking Packs \times Age ³	8.197E-10	1.620E-10	<0.0001		
		Covariate X	0.0006919	0.0006221	0.2660	1.001	(0.999 – 1.002)
$\rho = +0.1$	2542085.2	Smoking Packs	-0.0001236	0.0000438	0.0048		
		Smoking Duration	0.00759	0.0002129	<0.0001	1.008	(1.007 – 1.008)
		Years Since Cessation	-0.00635	0.0002737	<0.0001	0.994	(0.993 – 0.994)
		Smoking Packs \times Age	8.584E-06	2.065E-06	<0.0001		
		Smoking Packs \times Age ²	-1.528E-07	3.192E-08	<0.0001		
		Smoking Packs \times Age ³	8.197E-10	1.621E-10	<0.0001		
		Covariate X	0.0006027	0.0006278	0.3370	1.001	(0.999 – 1.002)
$\rho = +0.5$	2542084.0	Smoking Packs	-0.0001256	0.0000439	0.0042		
		Smoking Duration	0.00777	0.0002024	<0.0001	1.008	(1.007 – 1.008)
		Years Since Cessation	-0.00614	0.0002695	<0.0001	0.994	(0.993 – 0.994)
		Smoking Packs \times Age	8.670E-06	2.066E-06	<0.0001		
		Smoking Packs \times Age ²	-1.539E-07	3.193E-08	<0.0001		
		Smoking Packs \times Age ³	8.244E-10	1.621E-10	<0.0001		
		Covariate X	-0.00103	0.0007114	0.1487	0.999	(0.998 – 1.000)
$\rho = +0.9$	2542047.9	Smoking Packs	-0.0001335	0.000044	0.0024		
		Smoking Duration	0.00775	0.0001926	<0.0001	1.008	(1.007 – 1.008)
		Years Since Cessation	-0.00585	0.0002651	<0.0001	0.994	(0.994 – 0.995)
		Smoking Packs \times Age	9.067E-06	2.070E-06	<0.0001		
		Smoking Packs \times Age ²	-1.584E-07	3.197E-08	<0.0001		
		Smoking Packs \times Age ³	8.420E-10	1.622E-10	<0.0001		
		Covariate X	-0.00754	0.00122	<0.0001	0.992	(0.990 – 0.995)
$\rho = -0.1$	2542081.9	Smoking Packs	-0.000123	0.0000438	0.0050		
		Smoking Duration	0.00746	0.0002201	<0.0001	1.007	(1.007 – 1.008)
		Years Since Cessation	-0.00647	0.0002771	<0.0001	0.994	(0.993 – 0.994)
		Smoking Packs \times Age	8.564E-06	2.065E-06	<0.0001		
		Smoking Packs \times Age ²	-1.525E-07	3.192E-08	<0.0001		
		Smoking Packs \times Age ³	8.181E-10	1.621E-10	<0.0001		
		Covariate X	0.00128	0.0006269	0.0407	1.001	(1.000 – 1.003)
$\rho = -0.5$	2542064.6	Smoking Packs	-0.0001218	0.0000439	0.0055		
		Smoking Duration	0.00695	0.000249	<0.0001	1.007	(1.006 – 1.007)
		Years Since Cessation	-0.0069	0.0002925	<0.0001	0.993	(0.993 – 0.994)
		Smoking Packs \times Age	8.537E-06	2.065E-06	<0.0001		
		Smoking Packs \times Age ²	-1.519E-07	3.193E-08	<0.0001		
		Smoking Packs \times Age ³	8.144E-10	1.621E-10	<0.0001		
		Covariate X	0.00319	0.0006948	<0.0001	1.003	(1.002 – 1.005)
$\rho = -0.9$	2541980.5	Smoking Packs	-0.000117	0.0000439	0.0077		
		Smoking Duration	0.00469	0.0003518	<0.0001	1.005	(1.004 – 1.005)
		Years Since Cessation	-0.00879	0.0003567	<0.0001	0.991	(0.991 – 0.992)
		Smoking Packs \times Age	8.468E-06	2.066E-06	<0.0001		
		Smoking Packs \times Age ²	-1.498E-07	3.194E-08	<0.0001		
		Smoking Packs \times Age ³	7.992E-10	1.622E-10	<0.0001		
		Covariate X	0.00989	0.0009748	<0.0001	1.010	(1.008 – 1.012)

AIC = Akaike information criterion; CI = confidence interval; RR = relative risk (hazard ratio).

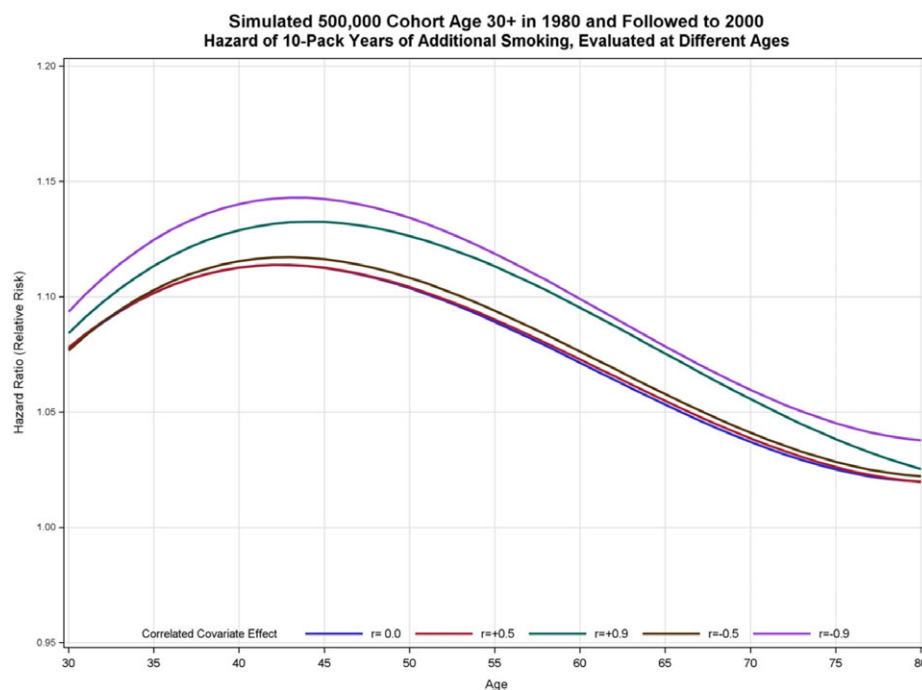


Fig. 4. Age-specific relative risk of death from all causes per 10 pack-years of cigarette smoking, adjusting for age, time-varying smoking (packs, duration, and time since cessation), interactions between smoking packs and age, and covariate X with varying degrees of correlation with packs smoked, in a simulated cohort of 500,000 men and women. The relative risk is modified by age, and the shape of the age-specific relative risk curve is not substantially affected by the direction or magnitude of the correlation between covariate X and smoking.

of correlation with covariate X. In all models, highly statistically significant independent associations were detected for duration of smoking (positive) and time since cessation of smoking (inverse) (Table II). Moreover, interactions between packs smoked and age, age squared, and age cubed were highly statistically significant in all models.

In models including interactions between smoking and age, the association with covariate X was negatively confounded with increasing strength of a positive correlation between covariate X and smoking (lowest RR = 0.992 with $\rho = +0.9$), and positively confounded with increasing strength of a negative correlation (lowest RR = 1.010 with $\rho = -0.9$) (Table II). The magnitude of bias in the estimated effect of covariate X was substantially smaller than in models that did not include smoking-by-age interactions (Table I).

4. DISCUSSION

Simulation studies have a long history in the epidemiologic and statistical literature. Specifically, in the context of air pollution epidemiology, simulations have been used in time-series studies to

investigate the impact of covariate measurement errors,^(29–31) confounding,⁽³²⁾ and convergence criteria for generalized additive models.⁽³³⁾ Simulations have also been used to evaluate the properties of the parameters of models generalizing marginal structural models.⁽³⁴⁾ White *et al.*⁽³⁵⁾ used simulations to investigate the impact of various measures of exposure to fine PM on hypertension within the framework of the Cox PH model. Not surprisingly, they concluded: “Metrics that incorporate exposure information from multiple years tend to be more robust and suffer from less bias. This study provides insight into factors that influence the metric used to quantifying exposure to fine PM and suggests the need for careful sensitivity analyses.” In our view, the sensitivity analyses should include an examination of the basic assumptions of the Cox PH model, which is what we have undertaken in this article. In the past,⁽³⁶⁾ we have used simulations to investigate the coverage properties of specific methods for the construction of CIs for parameters of the Cox PH model.

We used the SHG developed by the CISNET consortium of the NCI to generate a realistic cohort data set of all-cause mortality by smoking status in 500,000 men and women aged 30–70 years.

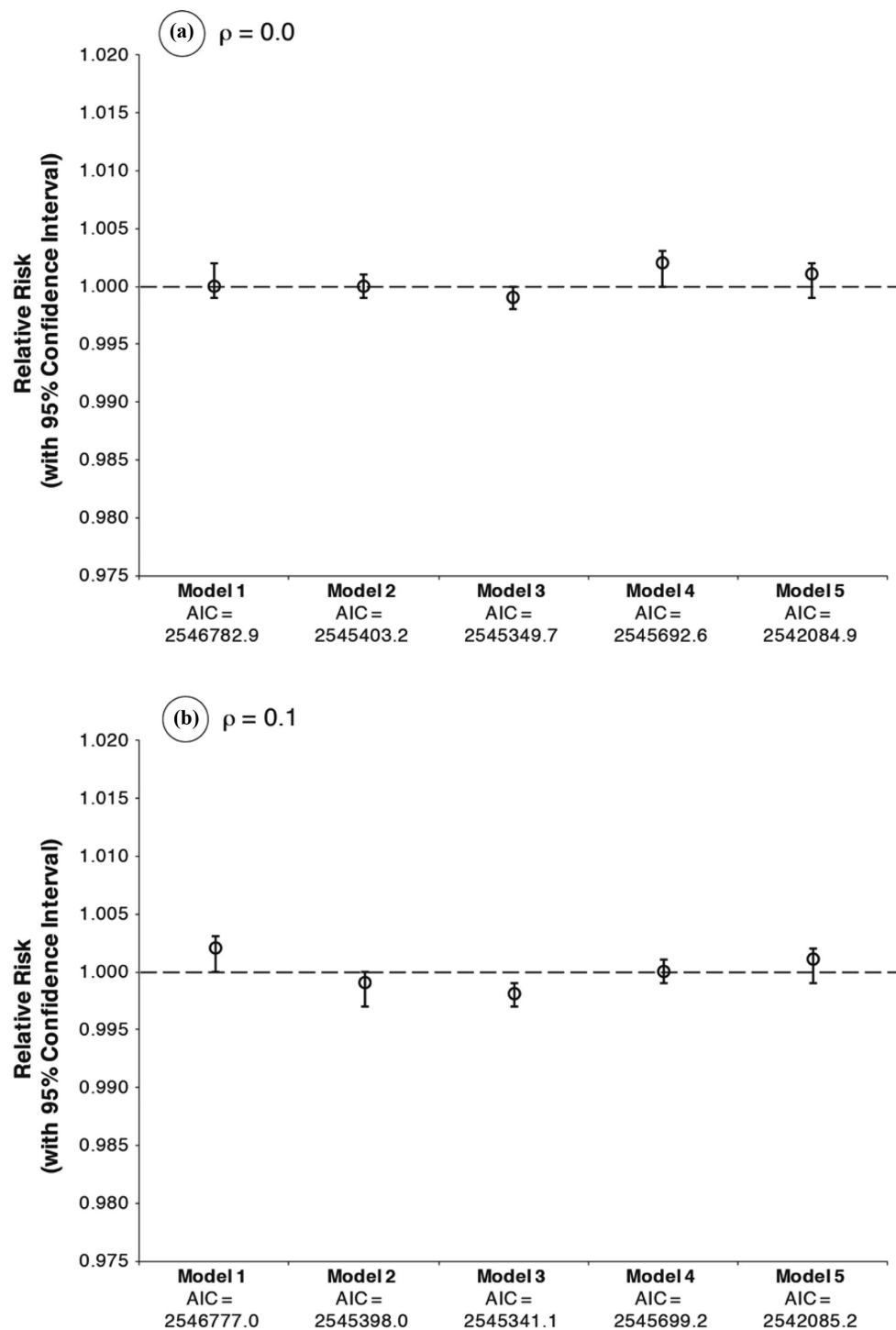


Fig. 5. Variation in the association (relative risk with 95% confidence interval) by Pearson correlation between smoking and covariate X ($\rho = -0.9$ to $+0.9$) and control for time-dependent smoking (models 1 to 5). Model 1: Smoking status only. Model 2: Smoking status and pack-years. Model 3: Smoking status, pack-years, and duration. Model 4: Smoking pack-years, duration, and time since cessation. Model 5: Smoking pack-years, duration, time since cessation, and pack-years \times age, age², and age³. Any divergence from a relative risk of 1.0 represents the magnitude of residual confounding due to inadequate control for smoking. AIC: Akaike information criterion. a: $\rho = 0.0$. b: $\rho = 0.1$. c: $\rho = 0.5$. d: $\rho = 0.9$. e: $\rho = -0.1$. f: $\rho = -0.5$. g: $\rho = -0.9$.

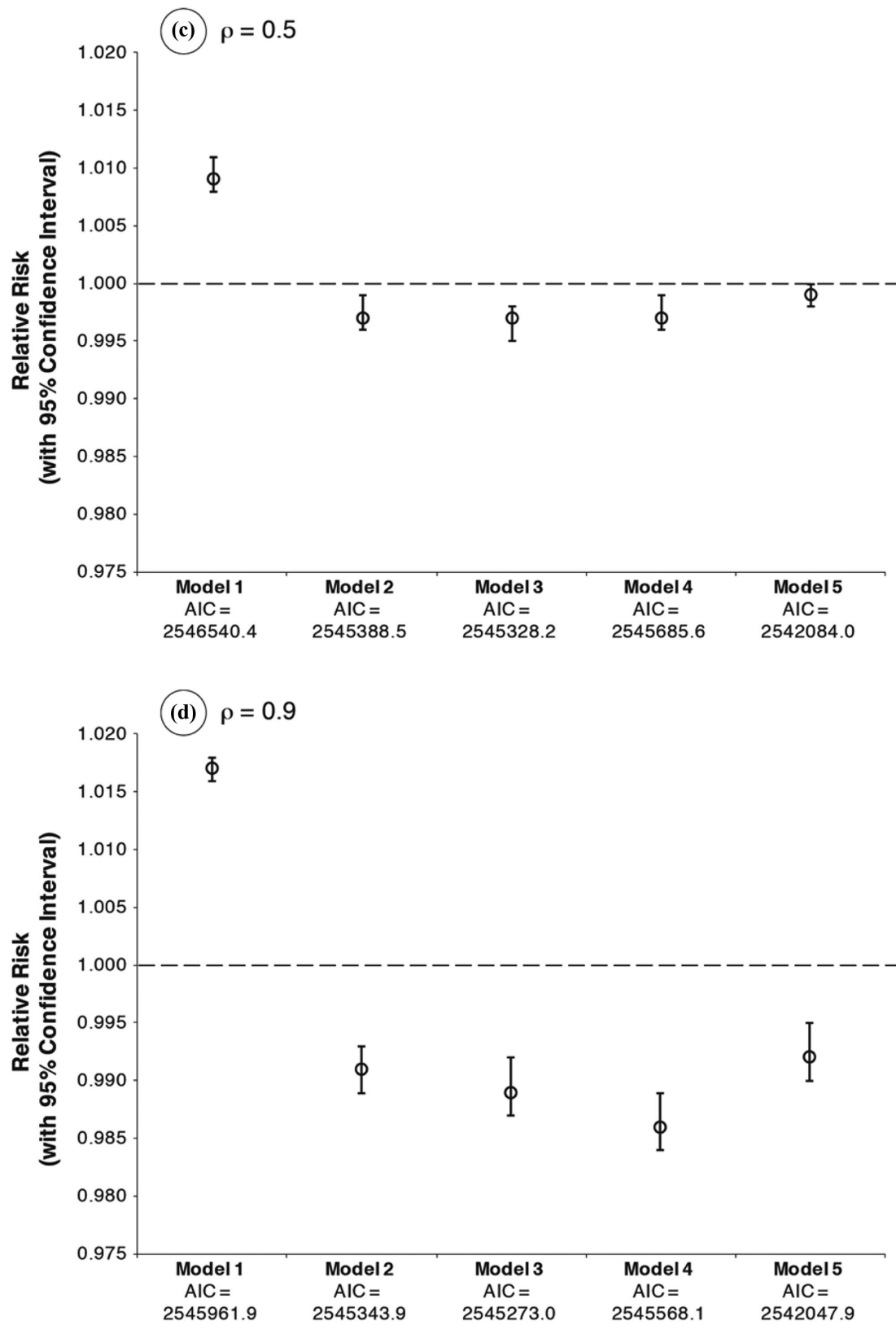


Fig. 5. Continued.

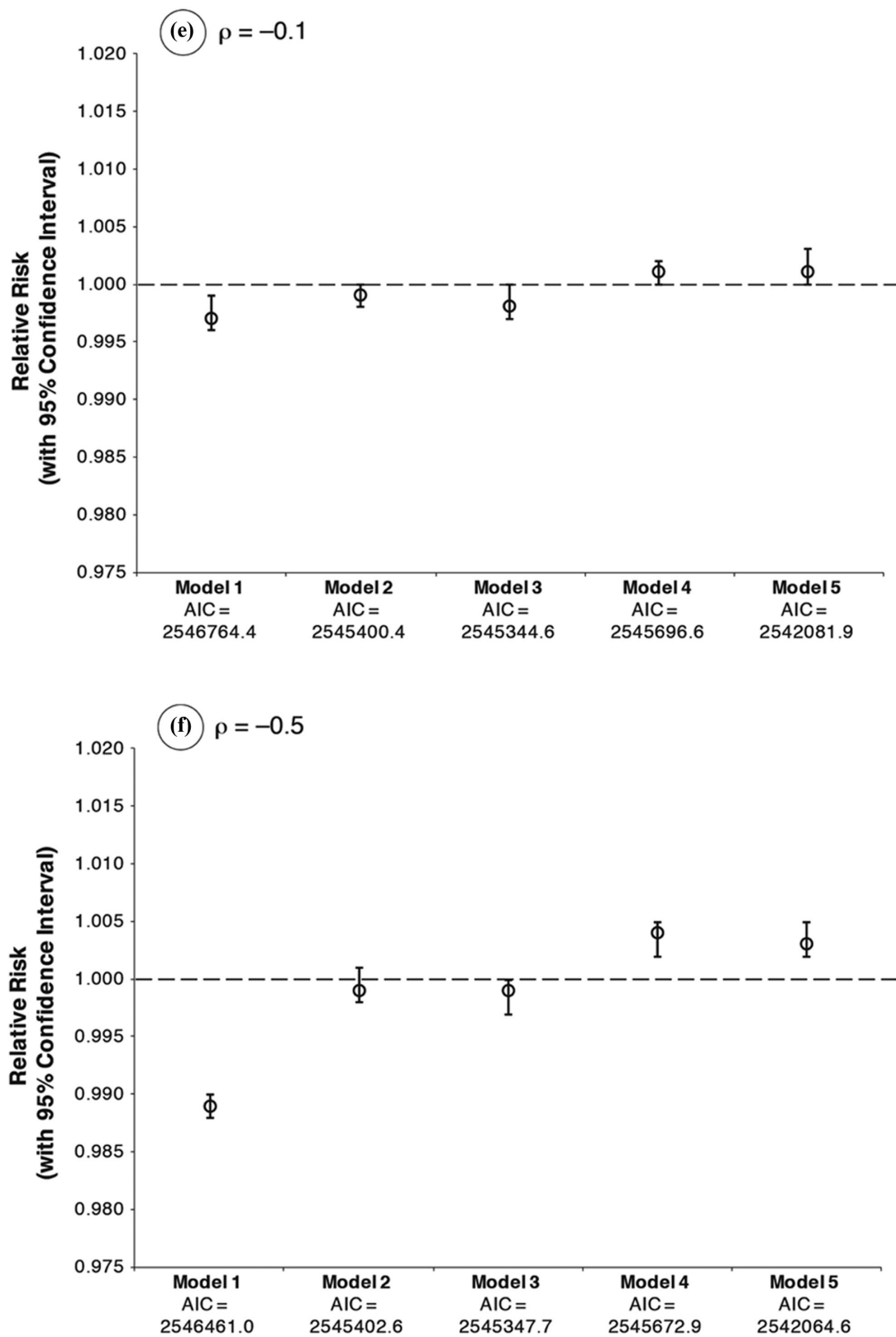


Fig. 5. Continued.

Using this data set, we explored the relationship of smoking with all-cause mortality and the ability of PH models with increasingly detailed exposure information to characterize this relationship and to adequately correct for smoking so that small RRs associated with other exposures can be estimated reliably.

As is the case for smoking-associated lung cancer, the risk of smoking-associated all-cause mortality is strongly modified by age, and this modification should be addressed in any analysis. We found also that cumulative exposure to smoking is not a good measure for the estimation of the RR, which depends additionally on temporal factors such as duration and time since cessation. We would have liked to include intensity of smoking and these two time-related factors in our analyses. There is, however, no obvious way in which smoking intensity can be used in a PH analysis because the partial likelihood contribution made by each risk set depends only on the value of covariates at the time at which the failure in the risk set occurs. As such, it has no memory of the covariate history unless it is incorporated directly into the functional form of the covariate at any time. Therefore, some function that captures changing intensities with time needs to be used, yet defining this function is not straightforward. Use of time-weighted average intensity has been suggested.⁽³⁷⁾ Another concern with using the PH model is that once temporal covariates are specified, the RR is assumed to depend only on the values of the covariates, and to be independent of the primary time axis. For example, if duration of smoking is included as a covariate, this covariate is assumed to be age invariant, i.e., independent of the actual ages at start and cessation. This is a strong assumption that is rarely tested.

From the AIC values shown in Table I, it is clear that model fit improves progressively with increasingly detailed incorporation of smoking information. The best fits are with time-dependent covariates that include cumulative exposure, duration of exposure, and time since cessation and with interaction terms for effect modification with age. Even with this elaborate control of smoking, however, the introduction of generated covariate X improves the fit further, suggesting that smoking is still inadequately controlled. Despite detailed time-dependent modeling of smoking including effect modification by age (Table II), we still obtained biased estimates of the impact of covariate X on mortality, suggesting that the use of PH models for analyses of data may often lead to spurious, difficult-to-interpret estimates of the risk associ-

ated with covariate X, whether or not that covariate is correlated with smoking.

These results based on a simulated cohort with a realistic distribution of smoking habits and smoking-related mortality reveal that with the traditional Cox PH approach to cohort data analysis, RR estimates for smoking and for a correlated covariate X change appreciably as smoking is better controlled. The direction of bias in the estimated impact of covariate X depends on the correlation structure between smoking and covariate X. As expected, the magnitude of confounding is greatest when the linear correlation between total packs smoked and covariate X is strongest; however, bias is evident even when the correlation is modest or nonexistent. Spurious RRs were on the order of 0.980 to 1.017 per 1-unit increase. This range encompasses, for example, the RRs reported for the associations between fine PM (RR = 1.17, 95% CI = 1.09–1.26 per 24.5- $\mu\text{g}/\text{m}^3$ increase [i.e., per 24.5-unit increase, as compared with our estimate per 1-unit increase]) or sulfates (RR = 1.15, 95% CI = 1.09–1.22 per 19.9- $\mu\text{g}/\text{m}^3$ increase) and all-cause mortality in CPS-II.⁽¹⁸⁾ Thus, bias due to the inability to adjust adequately for smoking could realistically account for at least some of the weak associations reported in the literature for fine PM and mortality.

Our analysis did not address the challenges introduced by multivariate confounding, that is, scenarios in which the confounding structure between cigarette smoking and covariate X is complicated by the presence of an additional important confounder, such as socioeconomic status.⁽³⁸⁾ We also did not consider scenarios involving effect modification across strata of another covariate. Furthermore, our analysis considered only simple linear correlations between cigarette smoking and covariate X. Our analysis also did not account for the use of ecologic measures of exposure (such as fine PM) and key confounders (such as neighborhood socioeconomic status). Finally, our results require confirmation in real-world cohorts with detailed, time-varying information on smoking.

In an article entitled “Epidemiology Faces its Limits,” science writer Gary Taubes suggested, based on conversations with prominent epidemiologists, that observational epidemiology studies were incapable of reliably detecting RRs less than 2.⁽³⁹⁾ In a series of articles, Ioannidis and colleagues have discussed the large number of false-positive results appearing in prestigious journals.^(40–44) Likewise, Boffetta and colleagues called for increased skepticism

and “epistemological modesty” in the interpretation and presentation of epidemiological findings in general, especially when they are new, unsupported by experimental or other epidemiological evidence, and detected among numerous comparisons.⁽⁴⁵⁾

While issues of covariate measurement error and confounding in epidemiological studies have been extensively discussed in the literature, there has been little or no discussion of the biases that could be introduced by the inherent structure of the PH model. Our results here show that the structure of the most commonly used methods for analyses of epidemiological data cannot reliably estimate small risks in epidemiological studies. Even for strong risk factors, such as cigarette smoking, the usual practice of using pack-years (i.e., cumulative exposure) as a measure of exposure yields imprecise information. It is reasonable to assume that any risks associated with exposure to air pollutants will depend likewise on both concentration and duration of exposure.

For analyses of cancer data, parametric models for hazard functions based on ideas of multistage carcinogenesis have been developed and refined for decades.^(5–7,25,46–51) Particularly when cohort data are available, the hazard functions rather than the ratio of hazard functions would appear to be the natural targets for estimation. These models can explicitly incorporate temporal factors in exposure and risk in analyses and thus address the issues that cannot be addressed with the PH model. Recent analyses evaluating the association between exposure to diesel engine exhaust and lung cancer mortality⁽⁵²⁾ have shown that explicitly considering temporal factors that are difficult to address with the PH model can lead to dramatically different conclusions. No comparable models are available for analyses of data on outcomes other than cancer. One way to extend these methods to outcomes other than cancer might be to use cumulative damage models with time-dependent parameters to perform a full likelihood-based analysis with contributions from each of the individuals in the cohort. The impact of various time-varying exposures to environmental agents could be introduced as described by Heidenreich *et al.*,⁽⁵³⁾ but presents difficult computational challenges.

In standard epidemiology textbooks⁽⁵⁴⁾ there is little or no discussion of the bias that can result from using the Cox PH model when the assumption of PH is violated as a consequence of effect modification by age or when temporal factors in exposure are important in determining risk. We believe that the single-minded focus on the PH model has hindered

the development of other approaches to analyses of epidemiological data. Epidemiologists may never have the methods to reliably estimate small risks from observational data; however, parametric alternatives to the PH model that directly estimate hazard functions rather than RRs and address the impact of time-varying exposure patterns on risk need to be developed.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Figures S1A–E. Comparison of overall survival rates between simulated cohort of 500,000 men and

women (“NCI,” solid line) and U.S. national mortality rates from the Social Security Administration (“US,” circular dots), stratified by sex (men = blue, women = red).

Figures S2A–D. Age-specific overall survival from age 35 years beginning in 1951 for current (continuing) smokers (solid red line) and never smokers (solid green line) in a simulated cohort, men only.

Figures S3A–B. Age-specific overall survival from age 60 years beginning in 1951 for current (continuing) smokers (red line) and never smokers (green line) in a simulated cohort, men only.

Figures S4A–B. Age-specific overall survival in 2004 for current (blue line), former (red line), and never smokers (green line) based on U.S. age-, sex-, and smoking-status-specific mortality rates calculated by Woloshin *et al.*

Table SI. All-cause mortality rate (deaths per 1,000) in a simulated cohort of 500,000 men and women from 1980 to 2000, nonsmokers

Table SII. All-cause mortality rate (deaths per 1,000) in a simulated cohort of 500,000 men and women from 1980 to 2000, light smokers

Table SIII. All-cause mortality rate (deaths per 1,000) in a simulated cohort of 500,000 men and women from 1980 to 2000, medium smokers

Table SIV. All-cause mortality rate (deaths per 1,000) in a simulated cohort of 500,000 men and women from 1980 to 2000, heavy smokers

Table SV. Results from Cox proportional hazards regression models for all-cause mortality including time-dependent smoking (packs smoked, duration of smoking, and time since cessation), covariate X, and interactions of attained age (age, age squared, and age cubed) with packs smoked and covariate X, with baseline hazards stratified by age and sex in a simulated cohort of 500,000 men and women; correlation shown is the Pearson correlation coefficient between packs smoked and covariate X