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Burden of smoking on cause-specific mortality: application to the Nurses' Health Study

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Abstract

Objective—The authors evaluated the burden of smoking on six causes of death in women using various novel modeling approaches.

Design—A prospective US-based nationwide cohort study.

Participants—102,635 women in the Nurses' Health Study followed biennially from 1980–2004.

Methods—The authors compared the relationship between cigarette-smoking and cause-specific death using baseline versus biennially-updated smoking status. They used competing risk survival analysis to formally compare associations of smoking-related variables on risk of death due to coronary heart disease (CHD), cerebrovascular diseases, lung cancer, other respiratory diseases, other smoking-caused cancers, and other causes.

Results—The associations of current and former smoking were stronger with most cause-specific mortality when using updated information. The effect of each smoking-related variable differed significantly ($p_h < 0.0001$) across some causes of death. For example, risks increased by 5% for death due to other causes up to 37% for lung cancer death for a 5-year earlier age at initiation. Compared with continuing to smoke, former smokers with 5 to 10 years of cessation had a 25% reduction in risk of dying from other causes of death up to a 61% reduction in risk of dying from CHD and cerebrovascular diseases.

Competing Interests: None

Conclusions—The risks of smoking and the benefits from quitting are greater than previously reported, when utilizing repeated measures of smoking data collected during follow-up, and vary by cause of death. Focused efforts to communicate the benefits of quitting to smokers and to prevent smoking initiation among children and youth should remain top public health priorities to reduce the worldwide mortality burden due to smoking.

Smoking causes many diseases and conditions, and remains the leading preventable cause of death in the United States.[1] Data describing the relation between smoking and mortality in women have been limited, as most studies focus on men and only collect smoking information once or twice over the follow-up period, [2–4] or have a short duration of follow-up.[5] After 22 years of follow-up in the Nurses' Health Study, we recently described the extent of the increase in risk of total and cause-specific mortality (including vascular diseases, respiratory diseases, cancers, and other causes) associated with current smoking and early age at smoking initiation, as well as the decrease in risk associated with smoking cessation.[6] In this and other smoking and mortality analyses, the relation between smoking and mortality appears to differ by cause, when evaluating one cause at a time.[6,7] The different relations between smoking and cause-specific mortality, as well as different rates of decline in risk after quitting, have not previously been formally compared using statistical approaches. In this report, we first evaluated whether updating smoking status is necessary for accurate estimates of the effect of smoking on mortality and then used the Lunn and McNeil method of competing risks analysis[8] to simultaneously and formally evaluate the effect of smoking factors on 6 causes of death: coronary heart disease (CHD), cerebrovascular diseases, respiratory diseases, lung cancer, other smoking-related cancers, and other causes.

METHODS

Study population

The Nurses' Health Study (NHS) cohort was established in 1976 when 121,700 female US registered nurses 30 to 55 years of age residing in 11 states completed a mailed questionnaire. Participants provided detailed information about medical history and risk factors for cancer, heart disease, and other diseases.[9] Since 1976, this information has been updated and extended on follow-up questionnaires mailed biennially. This study was approved by the Partners Human Research Committee (Boston, Massachusetts); completion of the self-administered questionnaire was considered to imply informed consent.

Assessment of smoking

On the initial 1976 questionnaire, participants reported whether they currently smoked or had ever smoked in the past and the age at which they started smoking. Current smokers reported the number of cigarettes smoked per day, and past smokers reported the age at which they stopped smoking and the number of cigarettes smoked per day before quitting. On each subsequent biennial questionnaire, participants reported whether they currently smoked cigarettes, and at the start of each 2-year follow-up cycle, were re-classified by their reported smoking status (never, past, or current), by quantity of cigarettes smoked and duration among current smokers, and by time since quitting among former smokers. If no follow-up questionnaire was returned, the most recent record of exposure status was carried forward for the subsequent interval. If a participant failed to return two consecutive questionnaires, smoking status was reclassified for that cycle and subsequent cycles if no additional questionnaires were returned as follows: never-smokers retained this status in all subsequent follow-up cycles, current smokers were classified as missing, past smokers who quit for >10 years retained their quitting status, and past smokers who quit for <10 years were classified as missing (recent quitters may not remain lifelong quitters). We classified

past smokers by categories of years since quitting, <5, 5 to <10, 10 to <15, 15 to <20 and 20+ years, and current and past smokers by cigarettes smoked per day, smoking duration, and age at smoking initiation.

Ascertainment of mortality

We started follow-up in 1980 because alcohol use and physical activity were not ascertained until that follow-up cycle. Deaths that occurred after the 1980 questionnaire was returned but before June 1, 2004 were grouped into 6 categories: (1) CHD (ICD 8th revision codes 410 to 414); (2) cerebrovascular diseases (codes 430 to 438); (3) respiratory diseases (codes 460 to 519); (4) lung cancer (code 162); (5) other smoking-caused cancers (cancers denoted by the 2004 Surgeon General's report to be caused by smoking[1]) including those of the lip, mouth, pharynx, esophagus (codes 140–150), larynx (code 161), pancreas (code 157), bladder and kidney (code 188–189), cervix (code 180), stomach (code 151), and acute myeloid leukemia (250); and (6) other causes, for example breast cancer, ovarian cancer, and colon cancer. Deaths were usually reported by families, and deaths among non-respondents were identified by searching the National Death Index.[10] We ascertained the cause of death and sought the pertinent medical records. Study physicians reviewed these records and the death certificate to classify individual causes of death without knowledge of information provided on the questionnaires. Only 6.1% of deaths were determined by death certificate information only.

Statistical analysis

Person-years of follow-up accrued from the date of return of the 1980 questionnaire until either the date of death or the end of follow-up (1 June 2004), whichever came first. Person-time for each 2-year follow-up period was equal to the number of months between the return of successive questionnaires, and was allocated to each variable based on the updated information provided by participants at the beginning of each follow-up cycle. Women contributed person-time only for follow-up periods for which they had complete smoking data. They were excluded in time periods where they were missing smoking data, which accounted for only 5.8% of the total follow-up time. We excluded participants with a prior history of cancer (other than non-melanoma skin cancer), vascular disease (myocardial infarction, angina confirmed by angiogram or stress test, a coronary artery surgery, or a stroke), or respiratory disease (including asthma, emphysema, or bronchitis) before baseline, leaving 102,635 participants available for follow-up.

Because of the different associations of age with each outcome, we used multivariable survival analyses with age as the time scale and allowed for different hazards of each type of outcome with age. We first implemented 2 modeling approaches to assess whether the type of smoking exposure assessment affected the estimates for smoking-related mortality. The first modeling approach used baseline smoking status and covariates, while the second approach allowed smoking status and covariates to be updated in each 2-year period. For example, a person who was a never smoker at baseline, started smoking in 1984, quit smoking in 1992, and started again in 1996, would be characterized as a never smoker according to the baseline-only analysis but would be classified as a current smoker in 1984, a past smoker in 1992, and a current smoker in 1996 in the updated analysis. To formally assess whether smoking had similar or different relations with the major causes of death, we then incorporated various smoking-related variables, specifically dose (in units of 10 cigarettes smoked per day) and smoking duration in current and former smokers, ever-smoking, age at initiation, and dose in ever-smokers, and time since cessation in former smokers into 2 different models (see Table 3). Inclusion of these specified variables was based on a previously published analysis that evaluated the impact of various ways of modeling smoking variables[11] and a recent commentary which highlighted the difficulties

in classifying the different dimensions of smoking exposure and the limitations of various approaches.[12] We implemented the approach described by Lunn and McNeil, [8] which stratifies on type of outcome and allows for the estimation of separate associations of each risk factor with the relative hazard of each outcome. This method uses data augmentation, assigning each participant a separate observation for each outcome. We coded the event variable as 1 (failed) if the participant died as a result of a specific cause of death corresponding to that data row, and as 0 otherwise; deaths were censored for the other causes of death at the time of death.

We included the following variables in our multivariate model because they were related to smoking status: body mass index (calculated using height, reported on the 1976 questionnaire, and body weight, which is updated with each biennial questionnaire), change in weight from age 18 to baseline, alcohol intake (categories of non-drinkers and drinkers of 0.1–4.9, 5.0–14.9, and 15.0+ grams/day), physical activity (quintiles based on MET hours/week), oral contraceptive use (never-, past-, current-user), postmenopausal hormone therapy (never-, past-, current-user), and parental history of myocardial infarction (MI) at or before age 65 years.[6] We also adjusted for history of hypertension, diabetes, and high cholesterol based on their established relation with mortality. Non-fatal diseases diagnosed during follow-up may affect subsequent smoking and act as an intermediate variable between smoking and mortality. For example, a person experiencing a non-fatal MI may reduce her smoking or quit smoking altogether, [13,14] and this MI (partly attributable to smoking) increases her risk of death. The extent of this type of confounding was evaluated in our first report on smoking and mortality by performing the G-computational algorithm.[15] In that analysis (which focused on smoking and CHD mortality), the risk estimates were identical to the crude estimates of risk, demonstrating that the magnitude of this problem is modest. In the primary analyses presented here, we attempted to address the problem of confounding by intermediate variables by stopping the updating of smoking and all covariates for those participants diagnosed with vascular disease, cancer, or respiratory disease. We used the covariate information provided in the period prior to diagnosis in all subsequent follow-up periods for these participants. Because non-fatal events may influence risk of death on other outcomes of interest, we also performed a secondary analysis updating all covariates to compare these results to those obtained when not updating covariates after non-fatal events.

Competing risk analysis

When comparing the hazard ratios for 6 categories of mortality, we assumed different associations of each smoking-related variable and covariates with each outcome (our null hypothesis). Starting with this full model, we decided a priori to first examine whether the relative hazards for each smoking variable varied between similar outcomes (1) CHD and cerebrovascular diseases; (2) lung cancer and other smoking-related cancers; (3) lung cancer and other respiratory diseases; and (4) respiratory diseases, lung cancer, and other smoking-caused cancers. For each of these 4 comparisons, we used a step-wise procedure and set the estimate of each smoking-related variable to be the same for those outcomes, while allowing the estimates of the remaining smoking-related variables to be different. We calculated the *p-value for* heterogeneity using a likelihood ratio test, with the degrees of freedom equal to the difference between the number of parameters in the full and reduced models. This stepwise procedure equated the association with the highest p-value (the p-value closest to 1), and then tested whether the remaining associations were similar or different, equating associations until the p-value for the test for heterogeneity was ≤0.05 for the remaining smoking-related variables. After developing this reduced model, we finally compared this model to a model with a single estimate for each smoking variable across causes of death using the step-wise procedure described above. In all of the models, the effects of all non-smoking-related risk factors were allowed to vary across the different causes of death. Using

the estimates from our final reduced model, we assessed the impact of initiating smoking 5 years earlier, using mortality rates from our population in age categories of 33–44, 45–54, 55–64, 65–74, and 75–82 years of age. For example, for those aged 65–74, we estimated the number of premature deaths for a 5-year earlier age at smoking initiation as: {(hazard for 5-year earlier age at smoking initiation - 1)} *(mortality rate for 65–74 age group)*(total person-years under consideration in the 65–74 age group).

All analyses were conducted using SAS software, version 9 (SAS Institute Inc, Cary, NC). All *P* values were based on 2-sided tests.

RESULTS

Table 1 shows age-standardized characteristics by smoking status at 3 time points over follow-up. The proportion of current smokers decreased from 28.1% in 1980 to 11.7% in 2000, while the proportion of past smokers who had quit for 20 or more years increased from 17.2% to 54.5% over this time period. With age-standardization, the percentage of participants with hypertension, diabetes, and high cholesterol increased over time, postmenopausal hormone use increased markedly, BMI increased and vigorous physical activity decreased. Our updated analyses capture these changes by the inclusion of these variables in our models.

Table 2 compares the relationship between smoking and cause-specific mortality when using baseline smoking status versus biennially-updated smoking status. There were 12,515 deaths in this cohort, with 1,390 due to CHD, 739 due to cerebrovascular disease, 759 respiratory deaths, 1,238 lung cancer deaths, 868 smoking-related cancer deaths (excluding lung cancer), and 7,521 deaths due to other causes. The top 10 causes of death in the other causes category were breast cancer (N=1142), ovarian cancer (N=467), colon cancer (N=465), senile and pre-senile dementia (N=340), other cancer: site not specified (N=328), other ill-defined and unknown cases of morbidity and mortality (N=296), other neoplasms of lymphoid tissue (N=254), sudden death (N=214), diabetes mellitus (N=202), and brain cancer (N=198). The association between current and former smoking and risk of death became stronger for each cause of death (except the association between former smoking and risk of CHD death) when using updated smoking status, as we anticipated. When updating, participants who stopped smoking during follow-up would be reclassified as former smokers, revealing the increased magnitude of the effect of current smoking on mortality; adding recent quitters to the former smoker group would increase the magnitude of the effect of former smoking on mortality. Because the decline in risk of dying from CHD is so rapid in recent quitters, we would expect to see similar estimates for former smoking when using baseline versus updated smoking status (HR=1.22 versus 1.16, respectively).

Table 3 summarizes the association between smoking factors and six major causes of mortality. The magnitude of the association was statistically similar for each smoking factor for CHD and cerebrovascular diseases except for smoking duration in former smokers (Model 1). In contrast, when comparing estimates of the smoking factors in Model 1 and Model 2 on lung cancer to other smoking-caused cancers, the magnitude of the association was different for all smoking variables except for dose in ever-smokers (Model 2). The effect of dose on respiratory diseases, lung cancer, and other smoking-caused cancers was similar when including ever-smoking, age at initiation and time since quitting in the model (Model 2), and amounted to a 24% increase in risk per 10 cig/day (95% CI 1.16 to 1.33). When comparing the estimates of the smoking factors on lung cancer to other respiratory diseases, the magnitude of the association was similar for dose in all smokers (Models 1 and 2) and duration only in former smokers (Model 1). Of note, the factors that differed were ever-smoking, duration of smoking in current smokers, earlier age at initiation in ever-

smokers, and time since cessation (Models 1 and 2) which had stronger effects on the risk of lung cancer death compared to deaths due to other respiratory diseases.

After developing our reduced model using the step-wise procedure (see Methods section), we used a final step-wise procedure to test whether the estimates presented in Table 3 could be reduced to one estimate for each smoking-related variable in the two models (the 4 variables in Model 1 and 4 variables in Model 2). The p-values for the test of heterogeneity were highly significant for each of the smoking variables ($p_h < 0.0001$), indicating that the effect of each smoking-related variable differed significantly across some causes of death. When modeling both dose and duration together, the effect of dose among current smokers was consistently strong across all outcomes, including deaths due to other causes, and the effect of dose and duration remained greatly elevated among former smokers on the risk of dying from respiratory diseases and lung cancer, as expected (Model 1). When including ever-smoking in the model, age at initiation, dose, and time since cessation each had independent effects on causes of death (Model 2), except for dose on cardiovascular deaths. Ever-smoking was associated with a 2 to 24-fold increased risk of death, depending on the cause. Initiating smoking at an earlier age significantly increased risk of death. For a 5-year earlier age at initiation, for example age 14 versus 19, risks increased by 5 percent for death due to other causes up to 37 percent for lung cancer death. Compared with continuing to smoke, former smokers with 5 to 10 years of cessation had a 61% reduction in risk of dying from CHD and cerebrovascular diseases, a 32% reduction in risk of dying from respiratory diseases, a 53% reduction in risk of dying from lung cancer, a 30% reduction in risk of dying from other smoking-related cancers, and a 25% reduction in risk of dying from other causes of death.

When updating all variables over time, including after diagnosis (compared to our primary approach), the biggest change observed was an apparent increased risk of death among recent quitters. This is most likely due to the impact of the disease to induce quitting, as well as to an increased risk of death. This phenomenon (also known as the reverse causation effect, where the outcome – disease - affects the exposure – smoking - rather than the exposure affecting the outcome)[16] partially masked the potential beneficial effect of recent quitting for all outcomes except for cardiovascular death. We also found a stronger effect of smoking duration, as smokers accumulated longer smoking durations when updating over follow-up.

In our population, we estimate that an additional 1421 premature deaths, comprising 10.2% of what would have been the total number of deaths, would have resulted if smoking had been initiated 5 years earlier (Table 4). Lung cancer deaths were 2.6 fold higher than all the other smoking-caused cancer deaths combined, due to the almost 10-fold higher risk of ever-smoking on lung cancer death compared to death due to other smoking-caused cancers. Public health measures to prevent smoking initiation, especially among children and youth, are worthwhile because of the significant reduction in risk observed across all major causes of death with delayed initiation, even after adjusting for ever-smoking, dose, and time since cessation (Table 3, Model 2).

DISCUSSION

In this study we addressed two important issues related to estimating the burden of smoking on cause-specific mortality. Our first question was whether the use of updated information on smoking, rather than simply using the baseline assessment, would materially affect the risk estimates for smoking-related mortality. Our second aim was to use competing risk survival analysis to evaluate the impact of smoking on major causes of mortality simultaneously.

To address our first question, we evaluated the relation between smoking and mortality by first using baseline smoking data only and then using updated smoking data over the study follow-up. We observed stronger associations of smoking with most cause-specific mortality when using updated information. Based on these findings, it is apparent that many epidemiologic studies have underestimated the disease risk due to smoking when exposure was assessed only at baseline. This limitation is particularly acute for studies with long followup, in a setting where changes in smoking behaviors are frequent. It is difficult to precisely capture the dynamic effects of an individual's smoking behavior. In our study, we do not ask about quit attempts between the biennial follow-up questionnaires and therefore we cannot calculate the potential risk reduction that may occur within these time intervals. However, we can update participants' smoking status every 2 years. This enables more accurate evaluation of the detrimental effects from long-term smoking and the risk reduction over time from sustained cessation, especially since tobacco smoke contains numerous carcinogenic agents with both initiating and promoting activity. Prospective studies that do not update smoking status over time, [17] or update once over a long follow-up period (greater than 2 years), [3,4] are likely to underestimate the adverse effect of current smoking, as some smokers quit during follow-up, but will continue to be classified as current smokers. It is also likely that these studies underestimate the benefits of quitting, as successful smoking cessation may occur only after multiple quit attempts, and people resuming smoking would remain misclassified as past smokers yet have substantially higher risks due to their current smoking. In our study, quitting and re-uptake of smoking varied across intervals, with 11–17% of current smokers at a given interval becoming past smokers in the next 2-year interval and 1.5–6% of past smokers at a given interval resuming smoking in the next 2-year interval. Reflecting the removal of bias, the results in this and our previous report[6] indicate greater harms than previously realized for women who are current smokers and greater benefits due to more rapid declines in risk after cessation than observed in other studies of women[5,17] that do not update exposure information during follow-up. Because smokers are more likely to quit if they experience serious symptoms, the impact of reverse causation should be evaluated in studies that have multiple assessments of smoking.

Our second aim was to use competing risk survival analysis to evaluate the impact of smoking on major causes of mortality simultaneously. Large cohort studies have enumerated the harms with continued smoking and benefits of smoking cessation on the major causes of disease associated with smoking[2,7,18,19] but to our knowledge, no formal comparisons have been made to evaluate the similarity of the relations across outcomes. Glynn and Rosner compared risk factors for the competing risks of CHD, stroke, and venous thromboembolism, using the same methods for formal comparison used in this analysis, and found similar associations for current and former smoking for CHD and stroke among men. [20] Our results also suggest a similar effect of all the smoking-related factors for these two causes of death, except for smoking duration in former smokers, where the risk was marginally but significantly higher for stroke. In our study, the effects of dose and duration of smoking in a former smoker do not affect one's risk of CHD mortality, which is consistent with disease biology, and these findings could be used to motivate smokers to quit. A recent commentary, which summarized the evidence used in a 2002 International Agency for Research on Cancer monograph, stated that "smoking cessation had similar effects of reducing risk for the other main tobacco-related cancers and for the main non-neoplastic diseases caused by smoking."[21] This conclusion, however, was not based on any formal statistical testing. We found statistically different reductions in risk due to smoking cessation over time for all types of mortality examined except for a similar effect for CHD and cerebrovascular disease, where we observed a large 46% reduction in risk in the first 5 years of quitting compared to continuing to smoke, and more gradual reductions in risk after the first 5 years. Of interest, some smoking factors such as dose had similar

effects on risk of respiratory diseases (excluding lung cancer) and lung cancer, while other factors such as ever-smoking status and age at smoking initiation had much stronger effects for lung cancer risk. In our cohort of women born 1921–1946, the typical age of smoking initiation was 19; if the trends we observed for the impact of age at smoking initiation can be extrapolated, the findings bode poorly for the current generation of smokers who typically begin at age 14. Finally, when considering the entire burden of disease of smoking, although smoking has the greatest effect on lung cancer, equal to a 24-fold increased risk, we found that the number of smoking-attributable deaths due to vascular disease (coronary heart disease + cerebrovascular disease) is larger than for lung cancer, as the rates for coronary heart disease and cerebrovascular disease are so much higher.

In conclusion, the risks of smoking and the benefits from quitting are greater than previously reported, when utilizing smoking data collected regularly over follow-up, and vary by cause of death. Communicating the risks associated with continuing to smoke and the benefits of quitting to smokers, in addition to focused efforts to prevent smoking initiation, especially among children, should remain top public health priorities to reduce the worldwide mortality burden due to smoking.

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Table 1

Age-standardized characteristics by smoking status at 3 time points over follow-up of 102,635 women in the Nurses' Health Study

Characteristic	Smoking status	Year of follow-up		
		1980	1990	2000
Smoking status(%)	Never	46.1	46.6	47.4
	Former	25.8	35.8	40.9
	Current	28.1	17.6	11.7
Duration of smoking, mean (SD), y	Former	14.6 (0.06)	18.5 (0.10)	20.5 (0.11)
	Current	26.5 (0.06)	35.3 (0.10)	42.7 (0.13)
Pack-years of smoking, mean (SD), y	Former	12.6 (0.12)	15.8 (0.16)	17.6 (0.17)
	Current	27.3 (0.12)	37.7 (0.17)	43.7 (0.20)
Time since quitting smoking (%)	Former			
<5		22.3	17.7	9.7
5 to <10		16.7	16.2	10.2
10 to <20		43.7	23.9	25.7
20+		17.2	42.3	54.5
Body mass index, mean (SD)	Never	24.5 (0.05)	25.8 (0.07)	26.8 (0.07)
	Former	24.4 (0.05)	25.7 (0.07)	26.9 (0.07)
	Current	23.6 (0.05)	24.6 (0.07)	25.6 (0.09)
Hypertension, %	Never	5.7	16.9	31.8
	Former	6.0	17.6	33.7
	Current	5.3	15.5	30.0
Diabetes, %	Never	0.7	3.0	5.9
	Former	0.6	2.9	6.0
	Current	0.7	2.6	6.5
High cholesterol, %	Never	1.8	26.2	31.3
	Former	2.2	28.5	33.6
	Current	2.0	24.9	32.2
Postmenopausal hormone use, %	Never	13.0	34.3	62.1
	Former	14.6	37.8	68.0
	Current	16.1	34.8	64.0
Alcohol intake >15g/day, %	Never	4.9	3.2	3.6
	Former	12.2	8.4	9.4
	Current	14.4	10.4	11.1
Vigorous Exercise at least once per week with activity ≥4 METs, % (1980) or METs/week, mean, (SD) (1990 and 2000)	Never	25.1	14.3 (0.25)	15.9 (0.27)
	Former	30.7	15.5 (0.26)	16.7 (0.28)
	Current	23.0	12.5 (0.28)	12.7 (0.32)

Abbreviations: MET, metabolic equivalent task

Table 2

Cause-specific mortality using baseline versus updated smoking status among Nurses' Health Study participants

		Using Baseline Smoking Status Only		Using Updated Smoking Status	
		Age-adjusted HR (95% CI)	**Multivariable-adjusted HR* (95% CI)**	**Age-adjusted HR (95% CI)**	**Multivariable-adjusted HR* (95% CI)**
Current smoking†	CHD	2.58 (2.29, 2.91)	3.68 (3.22, 4.22)	3.65 (3.21, 4.14)	3.81 (3.33, 4.36)
	Stroke‡	2.33 (1.98, 2.75)	2.93 (2.44, 3.52)	3.08 (2.57, 3.69)	3.09 (2.56, 3.73)
	Resp.§	10.04 (8.18, 12.32)	10.94 (8.78, 13.64)	13.33 (10.76, 16.52)	14.39 (11.53, 17.95)
	Lung Cancer	17.83 (14.63, 21.7)	23.3 (19.0, 28.8)	24.2 (19.75, 29.6)	29.6 (24.0, 36.5)
	Smoking-related Cancers‖	2.16 (1.85, 2.51)	2.69 (2.26, 3.20)	2.68 (2.26, 3.17)	2.94 (2.45, 3.52)
	Other**	1.59 (1.50, 1.67)	1.82 (1.71, 1.93)	1.89 (1.78, 2.00)	1.93 (1.81, 2.05)
Former smoking†	CHD	1.05 (0.91, 1.22)	1.22 (1.05, 1.43)	1.11 (0.98, 1.38)	1.16 (1.01, 1.33)
	Stroke‡	0.97 (0.80, 1.19)	1.11 (0.90, 1.37)	1.16 (0.98, 1.38)	1.16 (0.97, 1.39)
	Resp.§	2.06 (1.60, 2.66)	2.29 (1.76, 2.98)	3.50 (2.82, 4.35)	3.78 (3.02, 4.72)
	Lung Cancer	2.87 (2.26, 3.65)	3.54 (2.77, 4.53)	5.18 (4.20, 6.39)	6.31 (5.08, 7.83)
	Smoking-related Cancers‖	1.12 (0.94, 1.34)	1.26 (1.05, 1.53)	1.23 (1.05, 1.44)	1.35 (1.14, 1.59)
	Other**	1.06 (1.00, 1.12)	1.11 (1.04, 1.18)	1.10 (1.05, 1.16)	1.13 (1.07, 1.19)

Abbreviations: Resp, respiratory disease

*Adjusted for age (months), follow-up period, history of hypertension, diabetes, high cholesterol levels, body mass index, change in weight from age 18 to baseline (1980), alcohol intake, physical activity, previous use of oral contraceptives, postmenopausal estrogen therapy and menopausal status, parental history of myocardial infarction before or at 60 years, and age at starting smoking

†Reference category consists of never-smokers

‡Includes ischemic stroke, subarachnoid hemorrhage, cerebral hemorrhage

§Includes acute and chronic bronchitis, asthma, emphysema, pneumonia, and other diseases of respiratory system, except lung cancer

‖Includes smoking-caused cancers (according to the 2004 Surgeon General's report): acute myeloid leukemia, bladder, cervical, esophageal, kidney, larynx, oral cavity and pharynx, pancreas, and stomach

**Other includes other causes of death not included in the other 5 mutually exclusive categories of death

Table 3

Final hazard ratios* using a competing risks model for six categories of mortality: deaths due to coronary heart disease, cerebrovascular diseases†, respiratory diseases‡, lung cancer, other smoking-caused cancers§, and other causes, among 102,635 women followed from 1980 to 2004, after equating the impact of smoking factors with similar effects on different causes of death

Outcome:		**Coronary heart disease**	**Cerebro-vascular diseases**	**Respiratory diseases**	**Lung cancer**	**Other smoking-caused cancers**	**Other causes**	***p-value***‖
Deaths in current smokers (n)		474	214	340	691	232	1656	
Deaths in former smokers (n)		421	246	306	438	310	2688	
Deaths in never smokers (n)		495	279	113	109	326	3177	
Model 1								
Smoking variable	**Unit/Category**							
Current smokers								
Dose	10 cig/day	1.31 (1.22, 1.40)		1.62 (1.53, 1.71)		1.36 (1.21, 1.53)	1.25 (1.20, 1.31)	<0.0001
Duration	10 years	1.15 (1.09, 1.22)		1.52 (1.42, 1.62)	1.68 (1.58, 1.79)	1.10 (1.00, 1.21)	0.96 (0.93, 1.00)	<0.0001
Former smokers								
Dose	10 cig/day	1.02 (0.95, 1.10)		1.32 (1.24, 1.41)		1.16 (1.05, 1.29)	1.04 (1.01, 1.08)	<0.0001
Duration	10 years	1.01 (0.94, 1.07)	1.13 (1.05, 1.21)	1.57 (1.48, 1.66)		1.04 (0.96, 1.13)	0.93 (0.91, 0.96)	<0.0001
Model 2								
Smoking variable	**Unit/Category**							
Ever smokers								
Ever-smoking**		4.14 (3.61, 4.75)		10.40 (8.20, 13.19)	24.4 (19.57, 30.5)	2.49 (2.04, 3.04)	1.83 (1.69, 1.98)	<0.0001
Age at initiation	5 years	0.86 (0.80, 0.93)		0.85 (0.76, 0.95)	0.63 (0.56, 0.71)	0.80 (0.70, 0.92)	0.95 (0.91, 0.98)	<0.0001
Dose	10 cig/day	1.04 (0.95, 1.13)			1.24 (1.16, 1.33)		1.10 (1.05, 1.16)	<0.0001
Former smokers								
Time since cessation***	< 5 years	0.54 (0.45, 0.66)		1.01 (0.80, 1.26)	0.66 (0.55, 0.79)	0.70 (0.52, 0.95)	0.89 (0.81, 0.99)	<0.0001
	5 to <10	0.39 (0.31, 0.49)		0.68 (0.51, 0.89)	0.47 (0.38, 0.58)	0.70 (0.52, 0.95)	0.75 (0.67, 0.84)	
	10 to <15	0.42 (0.34, 0.52)		0.52 (0.38, 0.71)	0.71 (0.50, 0.99)	0.54 (0.38, 0.76)	0.72 (0.64, 0.81)	
	15 to <20	0.37 (0.30, 0.47)		0.31 (0.22, 0.45)	0.16 (0.11, 0.22)	0.39 (0.27, 0.57)	0.65 (0.58, 0.73)	
	20+	0.23 (0.20, 0.27)		0.13 (0.10, 0.17)	0.08 (0.07, 0.11)	0.40 (0.32, 0.50)	0.52 (0.48, 0.56)	

*Adjusted for age (months), follow-up period, history of hypertension, diabetes, high cholesterol levels, body mass index, change in weight from age 18 to baseline (1980), alcohol intake, physical activity, previous use of oral contraceptives, postmenopausal estrogen therapy and menopausal status, parental history of myocardial infarction before or at 60 years

† Includes ischemic stroke, subarachnoid hemorrhage, cerebral hemorrhage

‡ Includes acute and chronic bronchitis, asthma, emphysema, pneumonia, and other diseases of respiratory system, except lung cancer

§ Includes smoking-caused cancers (according to the 2004 Surgeon General's report): acute myeloid leukemia, bladder, cervical, esophageal, kidney, larynx, oral cavity and pharynx, pancreas, and stomach

|| P-value for test of heterogeneity

** Reference category consists of never smokers

*** Reference category consists of current smokers

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Table 4

Impact of initiating smoking 5 years earlier on death*

		Mortality rates/100,000 PY						
Age	**Person-years**	**Coronary heart disease**	**Cerebro-vascular diseases**	**Respiratory diseases**	**Lung cancer**	**Other smoking-caused cancers**	**Other causes**	**# of premature deaths with 5-yr earlier age at smoking initiation:**
33–44	282213	1	4	1	2	5	55	**15**
45–54	681084	15	10	4	16	11	141	**131**
55–64	835346	50	20	18	52	32	280	**435**
65–74	436192	145	67	90	123	88	651	**607**
75–82	77718	299	257	242	197	167	1576	**233**
# of premature deaths with 5-yr earlier age at smoking initiation by cause of death:		**194**	**104**	**114**	**459**	**174**	**376**	**1421**

*The mean age at smoking initiation in our study is 19 years, so applying a 5-year earlier age at initiation across the entire population would on average move age at initiation to age 14. Bolded numbers in table are counts (not rates).