Smoking Cessation and Decreased Risks Of Total Mortality, Stroke, and Coronary Heart Disease Incidence Among Women: A Prospective Cohort Study[a]

Ichiro Kawachi, Graham A. Colditz, Meir J. Stampfer, Walter C. Willett, JoAnn E. Manson, Bernard Rosner, David J. Hunter, Charles H. Hennekens, and Frank E. Speizer

INTRODUCTION

Smoking Cessation in Relation to Total Mortality Rates

Former smokers are at lower risk of total mortality compared with continuing smokers (Doll and Hill, 1956; Hammond and Horn, 1958; Dunn et al., 1960; Best et al., 1961; Kahn, 1966; Hammond, 1966; Doll and Peto, 1976; U.S. Department of Health and Human Services, 1990). However, the time required for the risk of total mortality among quitters to reach the level of never-smokers differs among studies, ranging from 6 to 10 years in one study (LaCroix et al., 1991) to 15 or more years in other studies (Rogot and Murray, 1980; U.S. Department of Health and Human Services, 1990). Few previous studies have been able to examine the temporal relationship between smoking cessation and decline in mortality risk while adjusting for other smoking-related factors, such as age at starting and number of cigarettes smoked.

Data about women have been sparse. For example, some large prospective studies with data on smoking cessation have been based solely on men (Kahn, 1966; Doll and Peto, 1976; Rogot and Murray, 1980). The British Female Doctors Study (Doll et al., 1980) had insufficient data to characterize the relationship between time since quitting and decline in mortality.

To address some of these deficiencies in the literature, we analyzed the health benefits of smoking cessation in the Nurses' Health Study, a large prospective cohort of women in the United States (Myers et al., 1987; Willett et al., 1987; Colditz, 1990). Our results describe the timing and extent of decline in risks of total and cause-specific mortality for patients considering cessation.

[a] *This chapter (text, tables, and figures) is excerpted from three articles published previously. Please refer to Kawachi and colleagues (1993a, 1993b, and 1994) in the reference list at the end of this chapter.*

Smoking Cessation and Decreased Risk of Stroke

Smoking is an established risk factor for stroke in both men and women (Shinton and Beevers, 1989). Based on a review of the available evidence, a U.S. Surgeon General's report, *The Health Benefits of Smoking Cessation. A Report of the Surgeon General, 1990*, concluded that smoking cessation reduces the risk of both ischemic stroke and subarachnoid hemorrhage compared with continued smoking (U.S. Department of Health and Human Services, 1990).

However, the relationship of time since quitting with risk of stroke has been addressed in only a few studies. In a review of case-control and prospective studies, risk of stroke returned to the level of never-smokers following smoking cessation, but time since quitting ranged from less than 5 to 15 years (U.S. Department of Health and Human Services, 1990; Donnan et al., 1989; Wolf et al., 1988; Colditz et al., 1988).

We analyzed 12 years of followup data from the Nurses' Health Study (Colditz, 1990) to examine the benefits of smoking cessation in relation to stroke incidence. In particular, we sought to characterize the relationship of time since stopping smoking with reductions in total and specific subtypes of stroke.

Smoking Cessation and Decreased Risk of Coronary Heart Disease

Cigarette smoking is a well-established risk factor for coronary heart disease (CHD) in men and women (U.S. Department of Health and Human Services, 1983). Although cessation of smoking reduces morbidity and mortality from CHD (U.S. Department of Health and Human Services, 1990), there have been conflicting reports of the time required for the excess risk to return to the level of never-smokers.

Some of smoking's effects that increase CHD risk (for example, increased platelet activation, elevated carbon monoxide levels, and coronary artery spasm) are immediately reversible, but other effects are either irreversible or are only slowly reversible (for example, development and progression of atherosclerosis) (McBride, 1992). Hence, it is possible that the smoker who stops will experience a component of rapid decline in risk compared with those who continue to smoke and a further component of risk that gradually falls to the level of never-smokers.

The available prospective epidemiological data are predominantly in middle-aged men, and they suggest that smoking cessation is accompanied by a halving of CHD risk after 1 year. These data also show that an additional 15 years are required for the risk to decline to the level of never-smokers (U.S. Department of Health and Human Services, 1990). However, a recent prospective study in predominantly elderly subjects suggested that risk in former smokers returns to that of never-smokers within 5 years of cessation (LaCroix et al., 1991). Further, several case-control studies, limited to nonfatal myocardial infarction (MI), have suggested that the excess CHD risk among former smokers dissipates completely less than 5 years after cessation (Rosenberg et al., 1985 and 1990; Dobson et al., 1991).

In the present study, we analyzed 12 years of followup data from the Nurses' Health Study (Colditz, 1990) to examine the relationship of time since stopping smoking with reduction in CHD incidence and mortality in middle-aged women.

METHODS

The Nurses' Health Study Cohort

The Nurses' Health Study (Colditz, 1990) cohort was established in 1976, when 121,700 female registered nurses 30 to 55 years of age completed a mailed questionnaire requesting information about risk factors for cancer and CHD, including current and past smoking habits; history of myocardial infarction, angina, cancer, diabetes, hypertension, high serum cholesterol levels, and menopause; and parental history of myocardial infarction. In addition, questions were included on height, weight, postmenopausal use of hormones, and history of oral contraceptive use. Since 1976, followup questionnaires have been mailed every 2 years to update information on smoking behavior, other cardiovascular risk factors, and the diagnosis of major illness. If no questionnaire was returned during the followup years, the most recent record of exposure status was used for the subsequent followup interval (for smoking-related variables, this occurred in less than 0.5 percent of the cohort). Further details of the Nurses' Health Study (Colditz, 1990) have been described elsewhere (Hennekens et al., 1979; Stampfer et al., 1985).

Exposure Data

Women were categorized according to their smoking status as never-smokers, former smokers, or current smokers. Current smokers were further classified as using 1 to 4, 5 to 14, 15 to 24, 25 to 34, 35 to 44, or 45 or more cigarettes per day. On the 1976 questionnaire, smokers were asked the age at which they started to smoke. In the present analysis, current and former smokers were classified as starting smoking at younger than age 15, from 15 to 17, from 18 to 21, from 22 to 25, or at age 26 or older. For time since stopping, former smokers were categorized as having stopped for less than 2, between 2 and 4, between 5 and 9, between 10 and 14, or more than 15 years.

Alcohol intake may potentially confound the association between cigarette smoking and risk of total mortality and cardiovascular disease (CVD) because smokers tend to drink more, and alcohol intake reduces the risk of CVD mortality (Stampfer et al., 1988; Rimm et al., 1991). In 1980, we assessed average frequency of alcohol intake over the preceding year. The levels of alcohol intake were categorized into 0, 0.01-4.9, 5.0-14.9, 15.0-24.9, and 25.0-49.9 g/day. Our measure of alcohol intake has been validated as part of an overall validation study of the food frequency questionnaire, conducted within a random sample of 194 Boston participants (Colditz et al., 1987; Giovannucci et al., 1991). A high correlation (Spearman r = 0.86) was found between average daily intake of alcohol as assessed by 28 days of diet records and intake computed from the 1980 food frequency questionnaire.

Vigorous physical activity may similarly potentially confound the association between smoking and mortality, because smokers tend to exercise less and exercise reduces the risk of CVD (Berlin and Colditz, 1990). We identified women taking part in regular vigorous exercise by asking the following question in the 1980 questionnaire: "At least once a week, do you

engage in any regular activity similar to brisk walking, jogging, bicycling, et cetera, long enough to work up a sweat?" Activity level as assessed by self-reports of sweat-inducing episodes of exercise has been shown to be strongly correlated with resting heart rate (Washburn et al., 1987), obesity (Washburn et al., 1987; Washburn et al., 1990), and high-density lipoprotein cholesterol levels (Washburn et al., 1990).

Ascertainment of Endpoints

Total Mortality

For the analysis of smoking cessation and total mortality, the endpoints constituted deaths from all causes occurring after the date of return of the 1976 questionnaire but before June 1, 1988. The deaths were further grouped into four broad categories: total CVDs (*International Classification of Diseases: 8th revision. Tabular List* [*ICD-8*] codes 410-440 and 795); total cancers (*ICD-8* codes 140-207); total cancers, excluding lung cancer (*ICD-8* codes 140-161 and 163-207); and external causes of injury (all ICD "E" codes), which include accidents and suicides (U.S. Department of Health, Education, and Welfare, 1972).

The mortality surveillance included systematic searches of the National Death Index (Stampfer et al., 1984) and vital records of the States to discover deaths among women who did not respond during each questionnaire cycle. This search was supplemented by reports from next of kin and postal authorities. We estimate that more than 98 percent of the deaths in the cohort were ascertained by these methods (Stampfer et al., 1984).

The classification of individual causes of death was carried out by a physician review of death certificates. Deaths due to cancer, CVD, and external causes of injury were classified as confirmed if these were listed as the underlying causes on the death certificate.

Ascertainment of

Strokes were confirmed by medical records if they were characterized by a typical neurologic deficit, sudden or rapid in onset, lasting at least 24 hours, and attributable to a cerebrovascular event, according to criteria established in the National Survey of Stroke (Walker et al., 1981). Strokes were defined as incident if they occurred after the date of return of the 1976 questionnaire but before June 1, 1988.

Death due to stroke was ascertained by a physician review of hospital records or autopsy reports or the listing of stroke as the underlying cause on the death certificate. The ascertainment of death included a systematic search of State vital records and the National Death Index (Stampfer et al., 1984) to discover deaths among participants who did not respond during each questionnaire cycle. This search was supplemented by reports from next of kin and postal authorities. If death appeared to be from vascular causes, written permission was requested from the next of kin (subject to the regulations of vital records offices) to review the medical records. More than 98 percent of deaths in the cohort were estimated to have been identified by this method (Stampfer et al., 1984).

When nonfatal stroke was reported on a followup questionnaire, permission was sought to obtain and review the medical records. The review

was carried out by physicians blinded with respect to the risk factor status of participants. The followup rate for nonfatal events through 1988, calculated as a percentage of the total potential person-years of followup, was 94.4 percent for never-smokers, 94.8 percent for former smokers, and 92.4 percent for current smokers. The criteria of the National Survey of Stroke (Walker et al., 1981) were used to further categorize strokes as subarachnoid hemorrhage, intracerebral hemorrhage, or ischemic stroke.

Ascertainment of Coronary Heart Disease Incidence

Cases of CHD were defined as incident if they occurred after the date of return of the 1976 questionnaire but before June 1, 1988. Incident CHD was further categorized as nonfatal MI or fatal CHD. Nurses who reported having a nonfatal MI on a followup questionnaire were asked for permission to review their medical records. Nonfatal MIs were "confirmed" if they met the diagnostic criteria of the World Health Organization (i.e., symptoms plus either cardiac enzyme elevations or diagnostic electrocardiographic changes) (Rose and Blackburn, 1982). All record reviews were conducted by physicians blinded to exposure status. A myocardial infarction was defined as probable if medical records were not available but hospitalization was required and confirmatory information was obtained by interview or letter. The present analyses included definite and probable cases. Eighty-two percent of the total CHD cases included in the present study were "definite" by our criteria. The followup rate for nonfatal MI through 1988, calculated as a percentage of the total person-years of followup, was 94.4 percent for never-smokers, 94.7 percent for former smokers, and 92.4 percent for current smokers.

As for all other endpoints in the study, the ascertainment of death included a systematic search of State vital records and the National Death Index (Stampfer et al., 1984) to discover deaths among participants who did not respond during each questionnaire cycle. This search was supplemented by reports from next of kin and postal authorities. If death appeared to be from vascular causes, written permission was requested from the next of kin (subject to the regulations of vital records offices) to review the medical records. Fatal CHD was defined as fatal MI confirmed by hospital records or at autopsy or as CHD recorded on the death certificate if this was the underlying and most probable cause given and there was previous evidence of that condition. In no)nstance was the cause on the death certificate accepted without corroboration. Total coronary heart disease was defined as nonfatal MI plus fatal CHD.

Statistical Analysis The present analyses included 12 years of followup data from June 1976 to June 1988. The primary analysis used mortality (or incidence) rates with person-months of followup as the denominator. For each participant, person-months were allocated according to the 1976 exposure variables and were updated according to information on biennial followup questionnaires. For women who died, person-months were assigned according to the covariate status reported in the most recently completed questionnaire, and followup was terminated at the date of death.

Relative risks (RR's) were calculated as the rate of death in each smoking category divided by the corresponding rate in the reference category. For analyses evaluating the relative risk of mortality among current smokers, we used never-smokers as the reference category. To assess the impact on mortality risk among former smokers by time since stopping, we followed the suggestion of the 1990 U.S. Surgeon General's report (U.S. Department of Health and Human Services, 1990) and used current smokers as the reference category. All relative risks were age adjusted by 5-year intervals, and 95-percent confidence intervals (CI) were calculated (Miettinen, 1976). The attributable risk of mortality (i.e., the excess number of deaths per 100,000 person-years attributable to smoking) was calculated as the difference between the mortality rates between current or former smokers and never-smokers. When appropriate, we performed the Mantel test for linear trend across categories of smoking variables and reported the 2-tailed *p* values (Rothman and Boice, 1979). We also used proportional hazards models to simultaneously control for age, cigarette smoking, and other risk factors for CVD and cancer.

Previous reports have indicated that former smokers tend to have smoked fewer cigarettes per day (U.S. Department of Health and Human Services, 1990) and to have started smoking at an older age than continuing smokers (Myers et al., 1987). Thus, at any age of quitting, former smokers have less cumulative exposure to cigarettes, on average, than continuing smokers. Therefore, failure to adjust for differences in cumulative exposure between former and current smokers may exaggerate the benefits of cessation. Wherever appropriate, we adjusted the relative risks of death among former smokers by the daily number of cigarettes smoked and the age at which they started smoking.

We excluded from analysis all women who had reported angina, MI, stroke, and cancer (other than nonmelanoma skin cancer) at baseline. This left a total cohort of 117,001 women who were available for followup.

Assessment of Confounding by Intermediate Variables

In a prospective study of smoking and mortality involving repeated measurement of smoking status, nonfatal disease may act simultaneously as a confounding factor and an intermediate variable in the pathway between smoking and mortality (Robins, 1987 and 1989). For example, in analyzing the relationship between smoking and CHD mortality, intervening morbid events (such as nonfatal MI or angina) may act as a determinant of subsequent exposure to smoking as well as an independent risk factor for subsequent death from coronary heart disease.

We assessed the extent of such confounding by performing the G-computational algorithm, as described by Robins (1987 and 1989), on the relationship between cigarette smoking and fatal CHD, using nonfatal MI and angina in the analysis as the time-dependent covariates.

RESULTS

Characteristics of Smokers

In 1976, 43.3 percent of the cohort members were never-smokers, 23.5 percent former smokers, and 33.2 percent current smokers. By 1988, the corresponding proportions were 42.6 percent never-smokers, 35.3 percent former smokers, and 22.1 percent current smokers. Some but not all health-related habits were distributed similarly between never-, former, and current smokers (Table 1). For example, current smokers tended to engage less in vigorous exercise, have slightly lower body mass index, and were more likely to drink more than 15 g of alcohol per day.

Results for Total Mortality

Over the 12 years of observation, 2,847 deaths occurred during 1,374,556 person-years. These consisted of 566 deaths from CVDs; 247 deaths from lung cancer; 1,209 deaths from cancers, excluding lung cancer; 261 deaths from external causes of injury; and 564 deaths from other causes. The category of "External Causes of Injury" covers *ICD-8* codes E800-E999 and includes all deaths from accident, poisoning, suicide, and other trauma (U.S. Department of Health, Education, and Welfare, 1972).

Causes of Death

Risks of Current Smokers

Total Mortality. Compared with women who had never smoked, current smokers experienced higher rates of total mortality (age-adjusted relative risk, 1.86; CI, 1.71 to 2.03) (Table 2). The age-adjusted relative risk increased with the number of cigarettes smoked per day (p, trend < 0.0001). Women who smoked 35 to 44 cigarettes per day had a relative risk of total mortality of 2.42 (CI, 2.01 to 2.90), whereas women who smoked

Table 1
Distribution of various potential self-reported risk factors according to smoking status among 117,001 Nurses' Health Study participants[a]

Variable	Smoking Status		
	Never-Smoker	Former Smoker	Current Smoker
Percent of Subjects in 1980	43.2	26.4	30.4
Total Person-Years of Followup (1976-1988)	593,026	404,359	377,171
Pack-Years Smoked	0	17.1	33.8
Body Mass Index (kg/m^2)	24.2	24.0	23.3
Hypertension	16.3%	16.9%	14.9%
Diabetes	2.2%	2.3%	2.0%
High Cholesterol	5.0%	5.8%	5.5%
Parental Myocardial Infarction Before Age 60	13.1%	14.5%	15.1%
Postmenopausal Hormone Use	18.3%	19.6%	20.2%
Vigorous Exercise At Least Once Per Week	43.1%	47.3%	37.9%
Alcohol Intake >15 g Per Day	7.5%	16.7%	21.2%

[a] *Percentage prevalence of risk factors has been directly age standardized by 5-year age categories to the distribution of ages in the whole cohort in 1980.*

Table 2

Total and cause-specific mortality by daily amounts of cigarettes consumed among current smokers—age-adjusted and multivariate RR's

Event	Never-Smoker	Former Smoker	Current Smoker	Cigarettes Used/Day Among Current Smokers[a] 1-14	15-24	25-34	≥35
Total Mortality							
Cases	933	799	1,115	234	480	215	153
RR[b]	1.00	1.28	1.86	1.41	1.99	2.06	2.57
RR[c]	1.00	1.29	1.87	1.51	2.02	2.09	2.63
		(1.14-1.46)	(1.65-2.13)	(1.26-1.81)	(1.74-2.35)	(1.71-2.55)	(2.12-3.27)
Total Cardiovascular Diseases							
Cases	131	151	284	56	124	57	37
RR[b]	1.00	1.69	3.47	2.48	3.78	4.11	4.73
RR[c]	1.00	1.57	3.74	2.69	4.25	4.28	5.64
		(1.17-2.12)	(2.86-4.89)	(1.82-3.97)	(3.14-5.77)	(2.86-6.41)	(3.52-9.04)
Total Cancer, Including Lung							
Cases	516	438	502	95	233	93	67
RR[b]	1.00	1.26	1.51	1.03	1.73	1.60	1.99
RR[c]	1.00	1.28	1.42	1.05	1.68	1.62	1.95
		(1.08-1.52)	(1.20-1.67)	(0.82-1.35)	(1.29-2.17)	(1.26-2.08)	(1.40-2.70)
Total Cancer, Excluding Lung							
Cases	492	366	351	83	161	61	36
RR[b]	1.00	1.11	1.10	0.94	1.25	1.10	1.12
RR[c]	1.00	1.11	1.19	1.02	1.23	1.09	1.15
		(0.91-1.34)	(0.99-1.44)	(0.77-1.36)	(0.97-1.56)	(0.78-1.53)	(0.77-1.74)
External Causes of Injury							
Cases	90	68	103	27	28	20	24
RR[b]	1.00	1.16	1.69	1.60	1.12	1.83	3.92
RR[c]	1.00	1.26	1.73	1.83	1.25	1.95	4.19
		(0.83-1.89)	(1.25-2.41)	(1.07-3.13)	(0.73-2.16)	(1.03-3.69)	(2.33-7.55)

[a] *Cigarettes smoked per day were unknown for 33 cases, including 10 cardiovascular disease deaths, 4 lung cancer deaths, 10 cancers other than lung cancer, 4 accidents or suicides, and 5 deaths from all other causes.*

[b] *Age-adjusted RR—95-percent CI in parentheses.*

[c] *Multivariate RR, adjusted for age in 5-year intervals, followup period (1976 to 1978, 1978 to 1980, 1980 to 1982, 1982 to 1984, 1984 to 1986, or 1986 to 1988), body mass index, history of hypertension, high cholesterol levels, diabetes, parental history of myocardial infarction before age 60, postmenopausal estrogen therapy, menopausal status, past use of oral contraceptives, and age at starting smoking.*

Key: RR = relative risk; CI = confidence interval.

45 or more cigarettes per day had a relative risk of 3.57 (CI, 2.52 to 5.04). The attributable risk of total mortality in current smokers compared with never-smokers was 120 per 100,000 person-years. Approximately 37 percent of all deaths among current smokers in this cohort was attributable to cigarette smoking.

Cause-Specific Mortality. The age-adjusted relative risk of CVD mortality among current smokers was 3.47 (CI, 2.85 to 4.22), and risk increased with the daily number of cigarettes used (p, trend = 0.002) (Table 2). Women who smoked only 1 to 4 cigarettes per day had an elevated risk of death from CVD (relative risk, 2.13; CI, 1.20 to 3.79), and those who smoked 45 or more cigarettes per day had a relative risk of 6.35 (CI, 3.26 to 12.34).

For total cancer mortality, including lung cancer, the overall age-adjusted relative risk among current smokers was 1.51 (CI, 1.33 to 1.70), and risk increased with the daily number of cigarettes used (p, trend < 0.0001). However, when lung cancers were excluded, the relative risk of cancer mortality among current smokers was not statistically significantly elevated (RR, 1.10; CI, 0.96 to 1.26), and there was no dose-response relationship with the daily amount of cigarettes used (p, trend > 0.2) (Table 2). This finding was explained by the fact that breast and colorectal cancer, two of the most common cancers in this cohort, had no association with cigarette smoking. The relative risk of deaths due to breast cancer among current smokers was 0.87 (CI, 0.68 to 1.12) and was 1.01 for colorectal cancer (CI, 0.69 to 1.46). On the other hand, the weak association between current smoking and total cancer after excluding lung cancer did not preclude the presence of strong associations between smoking and mortality from the less common cancers of individual sites, for example, cancers of the buccal cavity and pharynx (6 cases among current smokers; age-adjusted RR, 5.0; CI, 1.2 to 20.7), esophagus (7 cases among current smokers; age-adjusted RR, 11.1; CI, 2.1 to 58.9), and pancreas (26 cases among current smokers; age-adjusted RR, 1.9; CI, 1.1 to 3.4).

The age-adjusted relative risk of death from external causes of injury among current smokers was 1.69 (CI, 1.28 to 2.24), and risk increased with the daily number of cigarettes used (p, trend = 0.001).

Multivariate Models. The associations of cigarette smoking with total and cause-specific mortality changed only slightly after we controlled for potential confounders (including history of hypertension, diabetes, high serum cholesterol, relative weight, parental history of MI before age 60, past use of oral contraceptives, postmenopausal estrogen therapy, and age at starting smoking) in multivariate proportional hazards models (Table 2).

Decline in Risk Among Former Smokers

Total Mortality. Compared with never-smokers, the age-adjusted relative risk of total mortality among former smokers was 1.28 (CI, 1.16 to 1.40) (Table 2). When we examined the relationship between time since quitting and the relative risk of total mortality, the risk among former smokers approached the level of never-smokers after 10 to 14 years of cessation (Table 3; Figure 1).

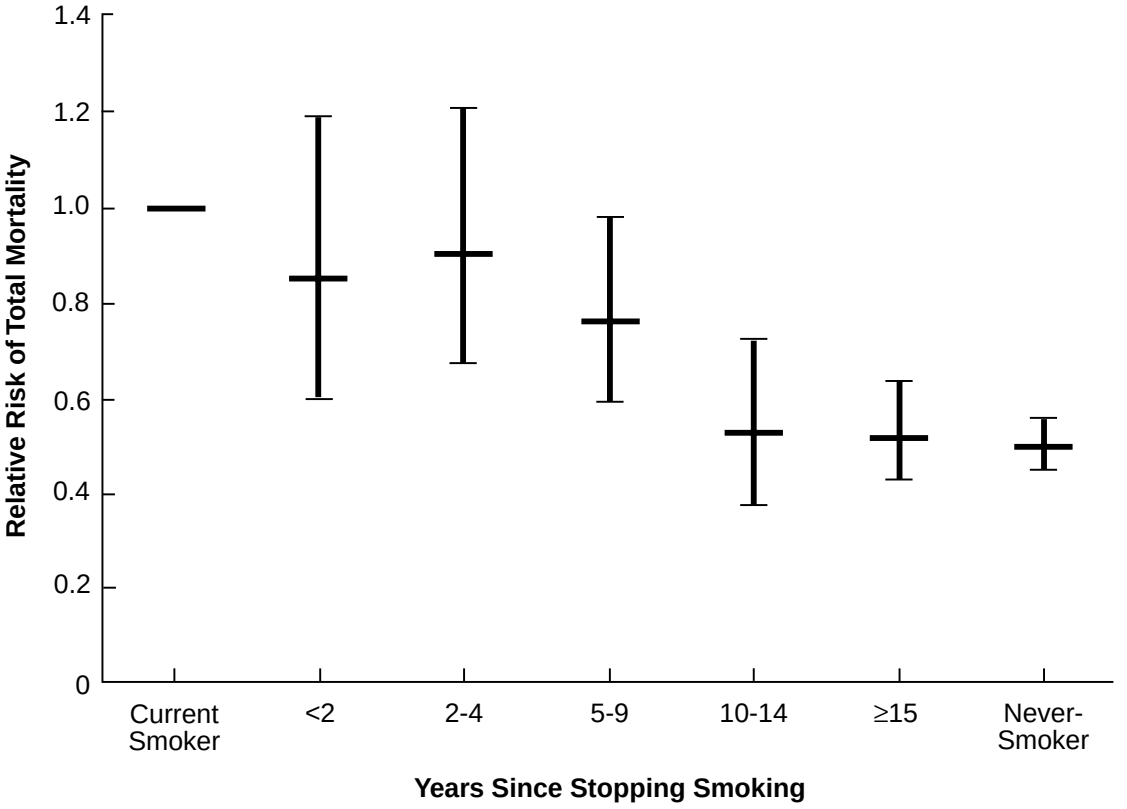
Table 3
Total and cause-specific mortality by time since quitting: Age-adjusted and multivariate RR's[a]

Event	Never-Smoker	Current Smoker	Years Since Quitting Among Former Smokers[b]				
			<2	2-4	5-9	10-14	≥15
Total Mortality							
Cases	933	1,115	127	106	131	66	231
RR[c]	0.54	1.00	1.08	0.90	0.72	0.48	0.59
RR[d]	0.56	1.00	1.19	1.00	0.79	0.53	0.61
	(0.52-0.62)		(0.95-1.50)	(0.79-1.28)	(0.63-0.99)	(0.39-0.71)	(0.51-0.74)
Total Cardiovascular Disease							
Cases	131	284	20	24	32	9	39
RR[c]	0.29	1.00	0.66	0.78	0.67	0.26	0.40
RR[d]	0.30	1.00	0.76	0.90	0.75	0.29	0.42
	(0.24-0.37)		(0.43-1.32)	(0.54-1.51)	(0.47-1.18)	(0.13-0.63)	(0.27-0.66)
Total Cancer, Including Lung							
Cases	516	502	75	48	69	37	134
RR[c]	0.66	1.00	1.42	0.90	0.84	0.60	0.78
RR[d]	0.72	1.00	1.56	1.00	0.93	0.69	0.81
	(0.64-0.81)		(1.16-2.10)	(0.70-1.42)	(0.69-1.27)	(0.46-1.03)	(0.64-1.04)
Total Cancer, Excluding Lung							
Cases	492	351	49	33	57	34	127
RR[c]	0.91	1.00	1.35	0.90	1.00	0.79	1.06
RR[d]	0.99	1.00	1.37	0.97	1.12	0.91	1.10
	(0.86-1.13)		(0.95-1.95)	(0.63-1.47)	(0.80-1.57)	(0.60-1.39)	(0.84-1.42)
External Causes of Death							
Cases	90	103	11	8	8	5	25
RR[c]	0.59	1.00	1.11	0.81	0.55	0.41	0.68
RR[d]	0.60	1.00	1.22	0.99	0.63	0.70	0.72
	(0.45-0.80)		(0.57-2.54)	(0.41-2.39)	(0.26-1.53)	(0.25-1.99)	(0.41-1.27)

[a] *Reference category consists of current smokers.*
Time since quitting was missing for 138 cases, including 27 cardiovascular disease deaths, 9 lung cancer deaths, 66 deaths from cancers other than lung, 11 accidents or suicides, and 25 deaths from all other causes.
[c] *Age-adjusted RR—95-percent CI in parentheses.*
[d] *Multivariate RR, adjusted for age in 5-year intervals, followup period (1976 to 1978, 1978 to 1980, 1980 to 1982, 1982 to 1984, 1984 to 1986, or 1986 to 1988), body mass index, history of hypertension, diabetes, high cholesterol levels, postmenopausal estrogen therapy, menopausal status, past use of oral contraceptives, parental history of myocardial infarction before age 60, and daily number of cigarettes smoked during the period prior to stopping smoking.*

Key: RR = relative risk; CI = confidence interval.

Figure 1
Risk of total mortality by time since quitting. Multivariate RR[a] of total mortality by time since quitting (reference category: current smokers). Error bars represent 95-percent CIs.



[a] *Nonfatal CHD, stroke, and cancer (except nonmelanoma skin cancer) were excluded at baseline and at the beginning of each successive 2-year followup period. Variables in model include age in 5-year categories, followup period (1976 to 1978, 1978 to 1980, 1980 to 1982, 1982 to 1984, 1984 to 1986, or 1986 to 1988), body mass index, history of hypertension, high cholesterol, diabetes, parental history of myocardial infarction before age 60, postmenopausal estrogen therapy, menopausal status, past use of oral contraceptives, age at starting smoking, and daily number of cigarettes consumed during the period prior to cessation.*

Key: RR = relative risk; CI = confidence interval.

In terms of absolute risk, if 1,000 women ages 40 to 44 years quit smoking today, approximately 17 deaths would occur over the next 14 years, compared with 30 deaths if they had continued smoking; that is, a net saving of 13 lives per 1,000 women over a 14-year period. The absolute benefits of cessation increase with age. Thus, if 1,000 women age 60 or older quit smoking today, approximately 103 deaths would occur over a period of 14 years compared with 138 deaths if they had continued smoking; that is, a net saving of 35 lives per 1,000 women.

A slight increase in relative risks was apparent in the category of former smokers who had quit for more than 15 years compared with those who had quit for 10 to 14 years. This was compatible with chance because the

95-percent CIs of the relative risks beyond 10 years of cessation excluded the point estimates of the risks among former smokers who had quit for shorter durations; however, we cannot exclude the possibility that a small excess in risk extends beyond 15 years of abstinence.

Cause-Specific Mortality. For CVD, a 24-percent reduction in the risk of mortality was apparent within 2 years of giving up cigarettes; however, the excess risk did not approach the level of never-smokers until 10 to 14 years after cessation. For deaths from external causes of injury, the age-adjusted relative risks among former smokers fell to the level of never-smokers 5 to 9 years after cessation (Table 3).

A greater risk of total cancer was observed among former smokers compared with current smokers in the first 2 years following cessation (age-adjusted RR, 1.42; CI, 1.12 to 1.81). The excess risk fell to the level of never-smokers 10 to 14 years after cessation. However, when lung cancer was excluded from the analysis of total cancer mortality, an excess risk was apparent only within the first 2 years of quitting (age-adjusted RR, 1.35; CI, 1.00 to 1.81) (Table 3).

The observations regarding the relationship of time since quitting with the risks of total and cause-specific mortality remained unchanged after controlling for potential confounding factors, including history of hypertension, diabetes, high serum cholesterol, relative weight, parental history of MI before age 60, past use of oral contraceptives, postmenopausal estrogen therapy, the daily number of cigarettes used, and age at starting (Table 3).

Age at Starting To Smoke

Current Smokers. We examined the relationship between age at starting and risk of total and cause-specific mortality among current smokers (Table 4). The relative risk of total mortality among current smokers who started smoking before age 15 was 2.80 (CI, 2.05 to 3.82), whereas for those who started after age 26 or older, the relative risk was 1.59 (CI, 1.28 to 1.97) (p, trend = 0.01). Starting smoking before age 15 was associated with the highest risk of death from CVD (age-adjusted RR, 8.72; CI, 5.58 to 13.65) and external causes of injury (age-adjusted relative risk, 3.22; CI, 1.37 to 7.55). Adjusting for multiple risk factors, including the daily number of cigarettes smoked, did not materially affect these observations (Table 4).

Former Smokers. Among former smokers the relationship between age at starting and the risks of total and cause-specific mortality was weaker and not statistically significant. These observations remained unchanged after adjusting for multiple risk factors, including the daily number of cigarettes consumed as well as time since quitting.

Assessment of the "Ill-Quitter" Effect

Previous studies have suggested that recent quitters include a disproportionate number of those who have quit because they are ill (U.S. Department of Health and Human Services, 1990). This causes a spuriously elevated risk of mortality among former smokers during the early years following cessation. To address this problem, we carried out

Table 4
Total and cause-specific mortality by age at starting smoking among current smokers: Age-adjusted and multivariate RR's

Event	Never-Smoker	Age at Starting To Smoke Among Current Smokers[a]				
		<15 Years	15-17	18-21	22-25	≥26 Years
Total Mortality						
Cases	933	38	175	657	149	88
RR[b]	1.00	2.80	1.86	1.88	1.95	1.59
RR[c]	1.00	3.15	1.85	1.77	1.86	1.45
		(2.16-4.59)	(1.51-2.28)	(1.54-2.03)	(1.50-2.32)	(1.15-1.92)
Cardiovascular Disease						
Cases	131	15	41	157	47	24
RR[b]	1.00	8.72	3.43	3.32	4.18	2.99
RR[c]	1.00	9.94	3.55	3.18	4.06	2.88
		(5.15-19.19)	(2.27-5.56)	(2.36-4.28)	(2.65-6.21)	(1.70-4.87)
Total Cancer, Including Lung						
Cases	516	11	77	300	73	38
RR[b]	1.00	1.46	1.48	1.54	1.70	1.23
RR[c]	1.00	1.64	1.43	1.43	1.69	1.10
		(0.84-3.20)	(1.06-1.93)	(1.18-1.74)	(1.24-2.29)	(0.75-1.62)
Total Cancer, Excluding Lung						
Cases	492	6	52	201	56	33
RR[b]	1.00	0.84	1.05	1.08	1.36	1.11
RR[c]	1.00	0.88	1.07	1.00	1.35	1.00
		(0.37-2.11)	(0.75-1.52)	(0.80-1.25)	(0.96-1.90)	(0.66-1.51)
External Causes of Death						
Cases	90	5	21	61	8	7
RR[b]	1.00	3.22	2.00	1.69	1.22	1.39
RR[c]	1.00	5.39	2.01	1.69	1.27	1.73
		(1.84-15.78)	(1.11-3.65)	(1.09-2.61)	(0.54-2.99)	(0.75-4.03)

[a] *Age at starting smoking was unknown for eight cases, including three deaths from cancers other than lung, one accident or suicide, and four deaths from all other causes.*

[b] *Age-adjusted RR—95-percent CIs in parentheses.*

[c] *Adjusted for age in 5-year intervals, followup period (1976 to 1978, 1978 to 1980, 1980 to 1982, 1982 to 1984, 1984 to 1986, or 1986 to 1988), history of hypertension, diabetes, high cholesterol levels, body mass index, past use of oral contraceptives, postmenopausal estrogen therapy, menopausal status, parental history of myocardial infarction before age 60, and daily number of cigarettes consumed.*

Key: RR = relative risk; CI = confidence interval.

analyses in which women who reported nonfatal CVD (MI, angina, stroke) or cancer (excluding nonmelanoma skin cancer) at each biennial questionnaire were excluded from further followup. These exclusions left 1,980 deaths for analysis (Tables 5 and 6). Among current smokers, the strength of the association between daily number of cigarettes and risk of total mortality increased after excluding diseases at the beginning of each 2-year interval (Table 5). When we examined the relationship of time since quitting with risk of cancer mortality (including and excluding lung cancer), there was no longer an excess risk apparent among former smokers within the first 2 years of quitting, suggesting an association between cancer diagnosis and stopping smoking (Table 6).

Assessment of Confounding by Intermediate Variables

As explained in "Methods," in a prospective study involving repeated measurement of smoking status, nonfatal disease may act simultaneously as a confounding factor and an intermediate variable in the pathway between smoking and mortality (Robins, 1987 and 1989). We assessed the extent of such confounding by applying a method previously described (Robins, 1987 and 1989) to the association between cigarette smoking and fatal CHD, with nonfatal MI as the intermediate variable. When we performed this analysis, the risk estimate of CHD mortality was virtually identical to the crude estimate of risk. Therefore, we concluded that confounding by intermediate variables was unlikely to be a concern in the present study.

Assessment of Confounding by Alcohol Intake and Vigorous Exercise

To examine the possible confounding effect of alcohol consumption and vigorous exercise on cigarette smoking, we analyzed data from the 1980 to 1988 followup interval. Although the analysis was limited to 2,356 deaths in total, the age-adjusted association between daily number of cigarettes used and risk of total mortality remained virtually unchanged. The relative risk of total mortality increased from 1.56 (CI, 1.28 to 1.91) among women using 1 to 14 cigarettes per day to 2.53 (CI, 1.95 to 3.24) among women using 35 or more cigarettes per day. After adjusting for alcohol consumption and vigorous exercise, the risk of total mortality among former smokers still declined to the level of never-smokers 10 to 14 years after cessation.

Adjusting for alcohol intake and vigorous exercise resulted in a slight strengthening of the association between current smoking and CVD mortality. For example, the multivariate relative risk of CVD mortality increased from 2.69 to 3.08 among women using 1 to 14 cigarettes per day and from 4.28 to 4.93 among women using 25 to 34 cigarettes per day. However, the excess risk of CVD death among former smokers still took 10 to 14 years to decline to the level of never-smokers.

The risk of death from external causes of injury among current smokers compared with never-smokers fell from 1.69 (CI, 1.28 to 2.24) to 1.54 (CI, 1.10 to 2.17) after adjusting for alcohol intake and vigorous exercise. The excess risk among former smokers still approached the level of never-smokers 5 to 9 years after cessation.

Table 5

Total and cause-specific mortality by daily number of cigarettes consumed. Comparison of analyses with and without 2-year exclusion of disease at the start of each period: Multivariate RR's

Event	Never-Smoker	Former Smoker	Cigarettes Used/Day Among Current Smokers			
			1-14	15-24	25-34	≥35
Total Mortality						
Cases[a]	933	799	234	480	215	153
RR	1.00	1.29	1.51	2.02	2.09	2.63
Cases[b]	632	410	176	381	175	130
RR	1.00	1.15 (1.01-1.29)	1.56 (1.26-1.94)	2.17 (1.82-2.59)	2.23 (1.77-2.80)	3.16 (2.49-4.02)
Cardiovascular Disease						
Cases[a]	131	151	56	124	57	37
RR	1.00	1.57	2.69	4.25	4.28	5.64
Cases[b]	111	106	47	114	52	33
RR	1.00	1.48 (1.13-1.94)	2.48 (1.61-3.82)	3.99 (2.84-5.59)	4.35 (2.83-6.69)	5.82 (3.50-9.69)
Total Cancer, Including Lung						
Cases[a]	516	438	95	233	93	67
RR	1.00	1.28	1.05	1.68	1.62	1.95
Cases[b]	262	172	51	168	64	50
RR	1.00	1.03 (0.85-1.26)	1.11 (0.76-1.62)	2.13 (1.62-2.81)	1.82 (1.24-2.65)	2.96 (2.03-4.34)
Total Cancer, Excluding Lung						
Cases[a]	492	366	83	161	61	36
RR	1.00	1.11	1.02	1.23	1.09	1.15
	244	140	43	100	33	22
RR	1.00	0.90 (0.73-1.11)	1.03 (0.68-1.55)	1.44 (1.05-1.99)	0.95 (0.58-1.57)	1.41 (0.82-2.40)

[a] *Cases and multivariate RR's after baseline exclusion of coronary heart disease, stroke, and cancer except nonmelanoma skin cancer. Multivariate RR were adjusted for age in 5-year intervals, followup period (1976 to 1978, 1978 to 1980, 1980 to 1982, 1982 to 1984, 1984 to 1986, or 1986 to 1988), body mass index, history of hypertension, high cholesterol levels, diabetes, parental history of myocardial infarction before age 60, postmenopausal estrogen therapy, menopausal status, past use of oral contraceptives, and age at starting smoking.*

[b] *Cases and multivariate RR's after exclusion of coronary heart disease, stroke, and cancer (except nonmelanoma skin cancer) at the beginning of each 2-year followup interval (95-percent CI in parentheses).*

Key: RR = relative risk; CI = confidence interval.

Table 6

Total and cause-specific mortality by time since quitting. Comparison of analyses with and without 2-year exclusion of disease at the start of each followup period: Multivariate RR's

Event	Never-Smoker	Current Smoker	Years Since Quitting Among Former Smokers				
			<2	2-4	5-9	10-14	≥15
Total Mortality							
Cases[a]	933	1,115	127	106	131	66	231
RR	0.56	1.00	1.19	1.00	0.79	0.53	0.61
Cases[b]	632	884	51	58	84	46	137
RR	0.49	1.00	0.76	0.73	0.70	0.47	0.49
	(0.44-0.54)		(0.53-1.08)	(0.53-1.01)	(0.53-0.92)	(0.33-0.67)	(0.39-0.62)
Cardiovascular Disease							
Cases[a]	131	284	20	24	32	9	39
RR	0.30	1.00	0.76	0.90	0.75	0.29	0.42
Cases[b]	111	254	11	11	23	7	33
RR	0.29	1.00	0.63	0.53	0.67	0.27	0.46
	(0.23-0.37)		(0.28-1.45)	(0.25-1.13)	(0.40-1.15)	(0.11-0.65)	(0.29-0.74)
Total Cancer, Including Lung							
Cases[a]	516	502	75	48	69	37	134
RR	0.99	1.00	1.37	0.97	1.12	0.91	1.10
Cases[b]	562	339	13	19	33	20	53
RR	0.54	1.00	0.42	0.66	0.75	0.56	0.51
	(0.46-0.64)		(0.20-0.89)	(0.38-1.16)	(0.49-1.16)	(0.33-0.96)	(0.35-0.74)
Total Cancer, Excluding Lung							
Cases[a]	492	351	49	33	57	34	127
RR	0.60	1.00	1.22	0.99	0.63	0.70	0.72
Cases[b]	244	201	9	11	25	18	50
RR	0.85	1.00	0.44	0.71	1.03	0.85	0.81
	(0.71-1.03)		(0.18-1.08)	(0.34-1.48)	(0.63-1.69)	(0.48-1.51)	(0.54-1.20)

[a] *Cases and multivariate RR's after baseline exclusion of coronary heart disease, stroke, and cancer except nonmelanoma skin cancer. Multivariate RR's were adjusted for age in 5-year intervals, followup period (1976 to 1978, 1978 to 1980, 1980 to 1982, 1982 to 1984, 1984 to 1986, or 1986 to 1988), body mass index, history of hypertension, diabetes, high cholesterol levels, postmenopausal estrogen therapy, menopausal status, past use of oral contraceptives, parental history of myocardial infarction before age 60, and daily number of cigarettes smoked during the period prior to stopping smoking (95-percent CIs in parentheses).*

[b] *Cases and multivariate RR's after exclusion of coronary heart disease, stroke, and cancer (except nonmelanoma skin cancer) at the beginning of each 2-year followup interval.*

Key: RR = relative risk; CI = confidence interval.

Results for Stroke Incidence

During the 12 years of observation, 448 incident cases of definite stroke occurred during 1,372,918 person-years. Theses consisted of 275 ischemic strokes, 108 subarachnoid hemorrhages, 53 cerebral hemorrhages, and 12 strokes that were classified as "unspecified."

Risks of Current Smokers

Compared with women who had never smoked, current smokers experienced substantially higher rates of stroke (Table 7). For all types of stroke combined, the overall age-adjusted relative risk among current smokers was 2.58 (95-percent CI: 2.08-3.19). However, the relative risks differed considerably for subtypes of stroke: 4.96 (95-percent CI: 3.13-7.87) for subarachnoid hemorrhage, 2.25 (95-percent CI: 1.72-2.95) for ischemic stroke, and 1.46 (95-percent CI: 0.77-2.78) for cerebral hemorrhage. The risk of stroke increased with the number of cigarettes smoked daily (Table 2). Within the category of smokers of 35 or more cigarettes per day, women who smoked 35 to 44 cigarettes per day had a relative risk of total stroke of 4.05 (95-percent CI: 2.78-5.91) compared with never-smokers, whereas women who smoked 45 or more cigarettes per day had a relative risk of 5.38 (95-percent CI: 2.59-11.18) (p, trend = 0.0004).

A statistically significant dose-response relationship also was found between daily cigarette consumption and the risk of ischemic stroke (p, trend = 0.03). There was a strong dose-response relationship between daily number of cigarettes smoked and risk of subarachnoid hemorrhage (Table 7). Within the category of smokers of 1 to 14 cigarettes per day, women who smoked 1 to 4 cigarettes per day had a relative risk of subarachnoid hemorrhage of 3.26 (95-percent CI: 1.03-10.33) compared with never-smokers, whereas women who smoked 5 to 14 cigarettes per day had a relative risk of 3.83 (95-percent CI: 1.88-7.80) (p, trend < 0.0004).

The association between cigarette smoking and total stroke, ischemic stroke, and subarachnoid hemorrhage persisted after control for potential confounders in multivariate proportional hazards models (Table 7). As expected, positive associations were found for known risk factors for stroke, such as history of high blood pressure (RR = 1.93, 95-percent CI: 1.51-2.48) and diabetes (RR = 3.57, 95-percent CI: 2.38-5.36). However, no associations were found between risk of total stroke and history of high serum cholesterol (RR = 0.99, 95-percent CI: 0.66-1.49), use of postmenopausal estrogen therapy (RR = 1.15, 95-percent CI: 0.88-1.51), or past use of oral contraceptives (RR = 1.12, 95-percent CI: 0.91-1.39). Too few cases of stroke (n = 2) occurred among current users of oral contraceptives to permit meaningful analysis.

Decline in Risk Among Former Smokers

The risk of total stroke for former smokers was intermediate between nonsmokers and current smokers (RR = 1.34, 95-percent CI: 1.04-1.73). In the analyses of the relationship of time since stopping smoking with risks of total stroke as well as various subtypes (Table 8), we used current smokers as the reference category. For less than 2 years after cessation, the age-adjusted relative risk among former smokers compared with continuing

Table 7

Age-adjusted RR's of stroke (fatal and nonfatal combined), by daily number of cigarettes consumed among current smokers

Event	Never-Smoker	Former Smoker	Current Smoker	Current Smoker: 1-14	15-24	25-34	≥35
Total Stroke							
Cases	126	114	208	40	92	38	34
RR[b]	1.00	1.34	2.58	1.79	2.84	2.70	4.23
		(1.04-1.73)	(2.08-3.19)	(1.26-2.54)	(2.19-3.67)	(1.91-3.84)	(2.99-6.00)
RR[c]	1.00	1.35	2.73	2.02	3.34	3.08	4.48
		(0.98-1.85)	(2.18-3.41)	(1.29-3.14)	(2.38-4.70)	(1.94-4.87)	(2.78-7.23)
Subarachnoid Hemorrhage							
Cases	19	25	64	13	21	17	11
RR[b]	1.00	2.01	4.96	3.68	4.05	7.31	8.28
		(1.12-3.61)	(3.13-7.87)	(1.91-7.11)	(2.30-7.14)	(4.15-12.85)	(4.45-15.42)
RR[c]	1.00	2.26	4.85	4.28	4.02	7.95	10.22
		(1.16-4.42)	(2.90-8.11)	(1.88-9.77)	(1.90-8.54)	(3.50-18.07)	(4.03-25.94)
Ischemic Stroke							
Cases	85	70	120	23	58	19	18
RR[b]	1.00	1.20	2.25	1.54	2.69	2.06	3.43
		(0.88-1.65)	(1.72-2.95)	(0.98-2.44)	(1.95-3.72)	(1.27-3.36)	(2.13-5.51)
RR[c]	1.00	1.27	2.53	1.83	3.57	2.73	3.97
		(0.85-1.89)	(1.91-3.35)	(1.04-3.23)	(2.36-5.42)	(1.49-5.03)	(2.09-7.53)
Cerebral Hemorrhage							
Cases	19	16	18	4	10	<-------- 4[d] ---------->	
RR[b]	1.00	1.27	1.46	1.18	2.01	1.18	
		(0.66-2.44)	(0.77-2.78)	(0.40-3.46)	(0.94-4.28)	(0.41-3.46)	
RR[c]	1.00	1.24	1.24	1.68	2.53	1.41	
		(0.64-2.42)	(0.64-2.42)	(0.34-5.28)	(0.71-6.05)	(0.39-5.05)	

[a] *Cigarettes smoked per day were unknown for four cases, including two subarachnoid hemorrhage and two ischemic stroke.*

[b] *Age-adjusted RR.*

[c] *Adjusted for age in 5-year intervals, followup period (1976 to 1978, 1978 to 1980, 1980 to 1982, 1982 to 1984, 1984 to 1986, or 1986 to 1988), history of hypertension, diabetes, high cholesterol levels, body mass index, past use of oral contraceptives, postmenopausal estrogen therapy, and age at starting smoking.*

[d] *These two categories were combined due to small numbers.*

Key: RR = relative risk.

smokers was 0.78, that is, a reduction in risk by 22 percent compared with continuing smokers. Nevertheless, this level of risk among former smokers was still about double that among never-smokers. During the interval between 2 and 4 years following cessation, the relative risk among former smokers was 0.46 (95-percent CI: 0.25-0.85). This indicated that almost 90 percent of the full potential benefit of cessation had occurred within those first 2 to 4 years, as the relative risk for never-smokers compared with current smokers was 0.39 (95-percent CI: 0.31-0.48) (Figure 2). Using never-smokers as the reference category, the age-adjusted relative risk of total stroke was 2.58 (95-percent CI: 2.08-3.19) among current smokers and was 1.17 (95-percent CI: 0.49-2.23) among former smokers who had stopped for 2 to 4 years. A similar pattern of decline was apparent after adjusting for other risk factors for stroke and daily number of cigarettes smoked in the followup period prior to stopping (Table 8).

To examine the possible confounding effect of alcohol consumption on cigarette smoking, we analyzed data from the 1980 to 1988 followup interval. Even after adjusting for alcohol consumption, the relationship of time since stopping smoking with risk of stroke remained virtually unchanged. Similarly adjusting for alcohol intake made virtually no difference to the relative risk estimate of daily number of cigarettes smoked and risks of stroke.

Subtypes of Stroke

Within subtypes of stroke, the number of events occurring in former smokers was small so that the age-adjusted relative risk estimates tended to be imprecise, with correspondingly wide 95-percent CIs. For ischemic stroke, the point estimate of the age-adjusted relative risk among former smokers fell by 46 percent compared with current smokers within the first 2 years after stopping, a fall that represented about 80 percent of the potential benefit of stopping smoking. The risk among former smokers returned to the level of never-smokers during the interval between 2 and 4 years following cessation. After adjusting for other risk factors for ischemic stroke as well as for the daily number of cigarettes consumed and the age at starting, between 60 and 70 percent of the potential benefit of cessation still occurred within 2 years of cessation (Table 8).

The risk of subarachnoid hemorrhage among former smokers similarly fell with increasing duration since cessation. After more than 5 years, the age-adjusted relative risk of subarachnoid hemorrhage among former smokers had returned to the level of never-smokers (RR = 0.24, 95-percent CI: 0.09-0.60). The few cerebral hemorrhages occurring among former smokers precluded our ability to carry out a meaningful analysis (Table 8).

Age at Starting To Smoke

We analyzed, separately for former and current smokers, the relationship of age at starting smoking with risks of stroke. Among current smokers, there appeared to be no relationship of the age at starting smoking with the age-adjusted relative risk of total stroke (p, trend = 0.76) or subtypes (Table 9). These findings remained unchanged after adjusting for other covariates, including the daily number of cigarettes consumed.

Table 8
Age-adjusted RR's of strokes (fatal and nonfatal combined), by time since quitting

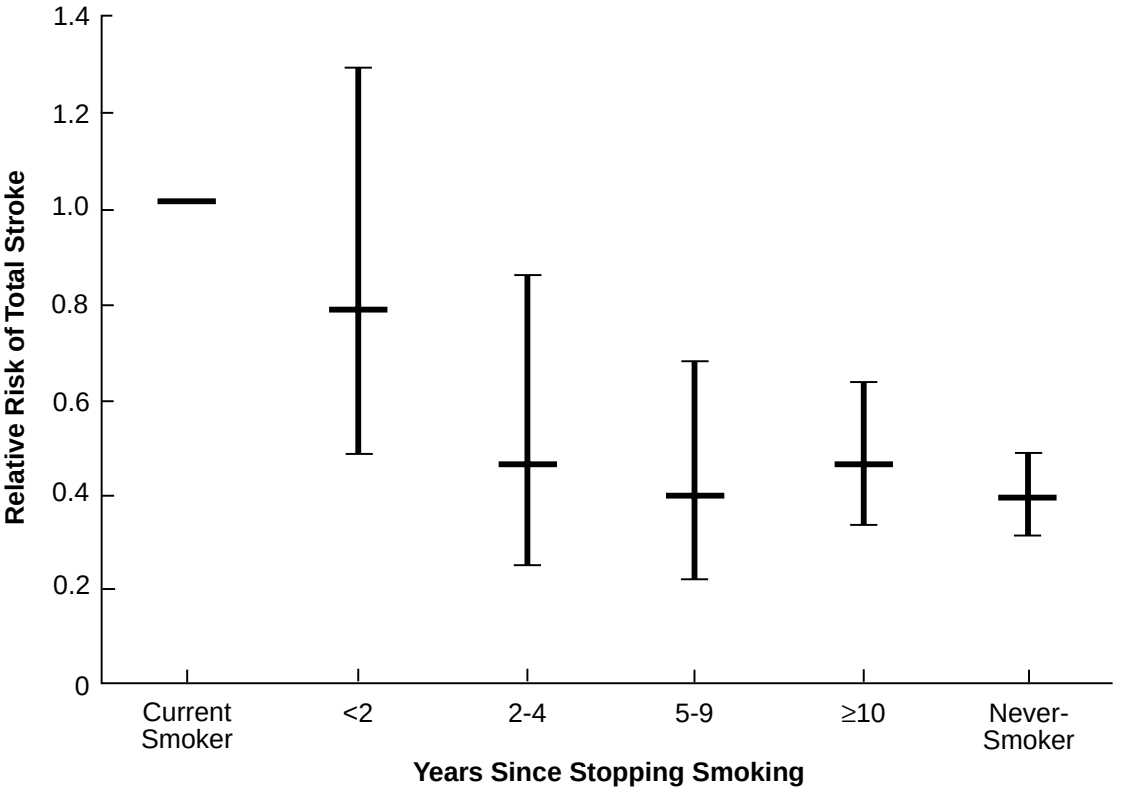
Event	Never-Smoker	Current Smoker	Years Since Quitting[a] <2	2-4	5-9	10-14	≥15
Total Stroke							
Cases	126	208	17	10	13	16	29
RR[b]	0.39	1.00	0.78	0.46	0.39	0.62	0.40
	(0.31-0.48)		(0.48-1.28)	(0.25-0.85)	(0.22-0.67)	(0.38-1.03)	(0.27-0.58)
RR[c]	0.37	1.00	0.73	0.59	0.39	0.60	0.39
	(0.29-0.46)		(0.40-1.33)	(0.28-1.21)	(0.20-0.77)	(0.32-1.12)	(0.24-0.64)
Subarachnoid Hemorrhage							
Cases	19	64	7	4	<------- 4[d] ------>		7
RR[b]	0.20	1.00	1.12	0.64	0.24		0.31
	(0.13-0.32)		(0.52-2.44)	(0.23-1.73)	(0.09-0.60)		(0.15-0.64)
RR[c]	0.21	1.00	1.12	0.84	0.26		0.34
	(0.12-0.34)		(0.42-2.99)	(0.25-2.78)	(0.08-0.85)		(0.13-0.90)
Ischemic Stroke							
Cases	85	120	7	3	11	11	15
RR[b]	0.44	1.00	0.54	0.23	0.55	0.73	0.36
	(0.34-0.58)		(0.26-1.15)	(0.08-0.66)	(0.30-1.02)	(0.39-1.34)	(0.21-0.60)
RR[c]	0.40	1.00	0.56	0.96	0.50	0.69	0.35
	(0.30-0.52)		(0.22-1.40)	(0.27-3.45)	(0.23-1.07)	(0.32-1.48)	(0.17-0.70)

[a] *Years since quitting was missing for 29 cases, including 3 subarachnoid hemorrhage, 23 ischemic stroke, and 3 cerebral hemorrhage.*
[b] *Age-adjusted RR.*
[c] *Adjusted for age in 5-year intervals, followup period (1976 to 1978, 1978 to 1980, 1980 to 1982, 1982 to 1984, 1984 to 1986, or 1986 to 1988), history of hypertension, diabetes, high cholesterol levels, body mass index, past use of oral contraceptives, postmenopausal estrogen therapy, and daily number of cigarettes consumed.*
[d] *These two categories were combined due to small numbers.*

Key: RR = relative risk.

By contrast, the earlier the age at starting among former smokers, the higher the age-adjusted relative risk of total stroke (p, trend = 0.01). This effect was caused mainly by the trend observed for ischemic stroke (p, trend = 0.01) but not for subarachnoid hemorrhage (p, trend = 0.55) (Table 10). These findings remained unchanged after adjusting for other covariates, including the daily number of cigarettes consumed as well as time since stopping. Too few cases of cerebral hemorrhage occurred among former smokers to permit analysis.

Figure 2
Risk of total stroke by time since quitting



Note: Age-adjusted relative risk of total stroke in relation to time since stopping smoking. Current smoker was the reference category. Error bars represent 95-percent confidence intervals.

Results for Coronary Heart Disease Incidence

During 12 years of followup, 970 incident cases of definite and probable CHD occurred during 1.37 million person-years. These included 745 cases of nonfatal MI and 225 cases of fatal CHD.

Risks Among Current Smokers

Compared with women who had never smoked, current smokers experienced substantially higher rates of CHD rates of CHD (Table 11). The age-adjusted relative risk among current smokers was 4.13 (95-percent CI: 3.04-5.63) for fatal CHD, 3.88 (95-percent CI: 3.28-4.58) for nonfatal MI, and 3.93 (95-percent CI: 3.39-4.55) for total CHD. Risk increased steeply with the number of cigarettes smoked so that women who smoked 45 or more cigarettes per day had age-adjusted relative risks of 10.00 (95-percent CI: 4.35-22.97) for fatal CHD, 4.64 (95-percent CI: 2.34-9.21) for nonfatal MI, and 5.74 (95-percent CI: 3.36-9.81) for total CHD. Even women consuming just 1 to 4 cigarettes per day doubled their risk of total CHD compared with never-smokers (age-adjusted RR = 1.94, 95-percent

Table 9
Age-adjusted RR's of stroke (fatal and nonfatal combined), by age at starting smoking among current smokers

Event	Never-Smoker	Age at Starting To Smoke Among Current Smokers[a]				
		<15 Years	15-17	18-21	22-25	≥26 Years
Total Stroke						
Cases	126	6	36	107	32	23
RR[b]	1.00	3.44 (1.60-7.41)	2.92 (2.04-4.18)	2.27 (1.76-2.92)	3.00 (2.08-4.34)	3.01 (1.97-4.59)
RR[c]	1.00	3.62 (1.41-9.28)	3.26 (2.00-5.31)	2.37 (1.68-3.35)	3.42 (2.09-5.61)	3.35 (1.98-5.68)
Subarachnoid Hemorrhage						
Cases	19	1	10	38	7	6
RR[b]	1.00	3.26 (0.50-21.34)	4.65 (2.30-9.38)	4.97 (3.03-8.16)	4.71 (2.14-10.37)	5.44 (2.39-12.35)
RR[c]	1.00	7.57 (0.68-84.07)	5.02 (1.90-13.24)	4.76 (2.50-9.08)	4.89 (1.74-13.75)	6.78 (2.21-20.81)
Ischemic Stroke						
Cases	85	4	21	58	19	16
RR[b]	1.00	3.53 (1.38-9.00)	2.62 (1.65-4.17)	1.86 (1.34-2.59)	2.60 (1.61-4.20)	3.07 (1.85-5.12)
RR[c]	1.00	5.96 (1.81-19.65)	3.16 (1.69-5.90)	2.08 (1.34-3.24)	3.15 (1.68-5.90)	3.79 (2.01-7.15)

[a] *Age at starting was missing for four cases, including two subarachnoid hemorrhage and two ischemic stroke.*
[b] *Age-adjusted RR.*
[c] *Adjusted for age in 5-year intervals, followup period (1976 to 1978, 1978 to 1980, 1980 to 1982, 1982 to 1984, 1984 to 1986, or 1986 to 1988), history of hypertension, diabetes, high cholesterol levels, body mass index, past use of oral contraceptives, postmenopausal estrogen therapy, and daily number of cigarettes consumed.*

Key: RR = relative risk.

CI: 1.23-3.08). To check the possibility that women who report smoking 1 to 4 cigarettes per day may represent a group who cut down from a previously high level of smoking, we reanalyzed the data by fixing smoking habits at baseline, that is, without updating the daily number smoked after each 2-year followup period. Smoking 1 to 4 cigarettes per day was still associated with a doubling of CHD risk (RR = 2.04, 95-percent CI: 1.32-3.16).

The strength of association between current cigarette smoking and total CHD remained unchanged after controlling for potential confounders, including body mass index, history of hypertension, diabetes, high cholesterol levels, previous use of oral contraceptives, use of postmenopausal estrogen therapy, menopausal status, parental history of MI before age 60, and age at starting smoking.

Table 10
Age-adjusted RR's of stroke (fatal and nonfatal combined), by age at starting smoking among former smokers

Event	Never-Smoker	Age at Starting To Smoke Among Former Smokers[a] <15 Years	15-17	18-21	22-25	≥26 Years
Total Stroke						
Cases	126	3	24	65	12	4
RR[b]	1.00	2.11 (0.69-6.45)	2.10 (1.37-3.22)	1.22 (0.91-1.65)	1.08 (0.60-1.95)	0.78 (0.29-2.10)
RR[c]	1.00	4.30 (1.15-16.00)	2.07 (1.22-3.51)	1.23 (0.85-1.80)	1.14 (0.57-2.28)	1.30 (0.48-3.52)
Subarachnoid Hemorrhage						
Cases	19	0	7	13	3	1
RR[b]	1.00	3.67 (1.63-8.25)	1.62 (0.80-3.25)	2.14 (0.65-7.06)	1.60 (0.22-11.50)	
RR[c]	1.00	1.78 (0.64-4.92)	1.65 (0.72-3.78)	3.96 (0.92-16.99)	9.21 (1.43-59.32)	
Ischemic Stroke						
Cases	85	3	15	37	9	2
RR[b]	1.00	3.21 (1.08-9.49)	2.00 (1.17-3.41)	1.03 (0.70-1.52)	1.16 (0.58-2.30)	0.54 (0.13-2.20)
RR[c]	1.00	7.27 (1.82-29.02)	1.97 (1.02-3.81)	1.02 (0.63-1.67)	1.14 (0.51-2.57)	0.81 (0.17-3.80)

[a] *Age at starting was missing for six cases, including one subarachnoid hemorrhage, four ischemic stroke, and one cerebral hemorrhage.*
[b] *Age-adjusted RR.*
[c] *Adjusted for age in 5-year intervals, followup period (1976 to 1978, 1978 to 1980, 1980 to 1982, 1982 to 1984, 1984 to 1986, or 1986 to 1988), history of hypertension, diabetes, high cholesterol levels, body mass index, past use of oral contraceptives, postmenopausal estrogen therapy, and daily number of cigarettes consumed.*

Key: RR = relative risk.

To examine the possible confounding effects of alcohol consumption and vigorous physical exercise on cigarette smoking, we analyzed data from the 1980 to 1988 followup interval. Controlling for these two additional variables resulted in little change in the strength of the observed association between smoking and total CHD risk.

Decline in Risk Among Former Smokers

Risk of CHD among former smokers was intermediate between never-smokers and current smokers. Compared with never-smokers, the age-adjusted relative risk among former smokers was 1.63 (95-percent CI: 1.11-2.40) for fatal CHD, 1.47 (95-percent CI: 1.19-1.83) for nonfatal MI, and 1.51 (95-percent CI: 1.25-1.82) for total CHD. The relationship of time since stopping with CHD risk was examined (Table 12). In Table 12, the "baseline" consists of persisting active smokers. Thus never-smokers are at approximately one-fifth the risk of total CHD compared with continuing

Table 11

Daily number of cigarettes smoked and age-adjusted and multivariate RR's of fatal coronary heart disease and nonfatal myocardial infarction, compared with never-smokers

			Cigarettes Smoked/Day Among Current Smokers[a]					
Event	Never-Smoker	Former Smoker	1-4	5-14	15-24	25-34	35-44	≥45
Fatal Coronary Heart Disease								
Cases	49	53	4	18	53	28	14	4
RR[b]	1.00	1.63	1.87	2.78	4.29	5.36	5.56	10.00
		(1.11-2.40)	(0.69-5.09)	(1.66-4.67)	(3.00-6.15)	(3.53-8.14)	(3.26-9.50)	(4.35-22.97)
RR[c]	1.00	1.62	<---- 2.85 ---->		4.85	6.96	<---- 7.84 ---->	
		(1.09-2.40)	(1.53-5.32)		(3.01-7.81)	(3.90-12.43)	(3.71-16.57)	
Nonfatal Myocardial Infarction								
Cases	166	161	15	56	189	95	54	7
RR[b]	1.00	1.47	1.97	2.46	4.21	4.87	5.58	4.64
		(1.19-1.83)	(1.17-3.30)	(1.83-3.29)	(3.48-5.11)	(3.87-6.13)	(4.24-7.35)	(2.34-9.21)
RR[c]	1.00	1.44	<---- 2.45 ---->		4.77	5.21	<---- 5.32 ---->	
		(1.16-1.79)	(1.69-3.56)		(3.64-6.26)	(3.73-7.28)	(3.61-7.86)	
Total Coronary Heart Disease								
Cases	215	214	19	74	242	123	68	11
RR[b]	1.00	1.51	1.94	2.53	4.22	4.97	5.57	5.74
		(1.25-1.82)	(1.23-3.08)	(1.96-3.26)	(3.56-5.00)	(4.06-6.08)	(4.36-7.11)	(3.36-9.81)
RR[c]	1.00	1.48	<---- 2.53 ---->		4.79	5.49	<---- 5.49 ---->	
		(1.22-1.79)	(1.84-3.50)		(3.78-6.08)	(4.10-7.35)	(3.87-7.77)	

[a] *Daily number smoked was missing for four cases, including two cases of fatal coronary heart disease and two nonfatal myocardial infarction.*

[b] *Age-adjusted RR.*

[c] *Adjusted for age in 5-year intervals, followup period (1976 to 1978, 1978 to 1980, 1980 to 1982, 1982 to 1984, 1984 to 1986, or 1986 to 1988), history of hypertension, diabetes, high cholesterol levels, body mass index, past use of oral contraceptives, menopausal status, postmenopausal estrogen therapy, and age at starting smoking.*

Key: RR = relative risk.

smokers. Within 2 years of cessation, the age-adjusted relative risk among former compared with current smokers was 0.53 (95-percent CI: 0.25-1.12) for fatal CHD, 0.85 (95-percent CI: 0.60-1.19) for nonfatal MI, and 0.77 (95-percent CI: 0.57-1.05) for total CHD. Although nearly one-third of the excess risk of total CHD was removed within 2 years of smoking, the risk among former smokers did not decline to the level of never-smokers until 10 years after cessation. This finding remained unchanged after adjusting for other cardiovascular risk factors, daily number of cigarettes smoked before stopping, and age at starting smoking.

To examine the possible confounding effects of alcohol consumption and vigorous physical exercise on the relationship of time since stopping with CHD risk, we analyzed data from the 1980 to 1988 followup interval. Controlling for these variables resulted in a slight increase in the relative risks of total CHD across categories of former smokers; however, it did not alter

Table 12
Time since quitting and age-adjusted and multivariate RR's of fatal coronary heart disease and nonfatal myocardial infarction, compared with current smokers

Event	Never-Smoker	Current Smoker	Years Since Quitting[a] <2	2-4	5-9	10-14	≥15
Fatal Coronary Heart Disease							
Cases	49	123	7	9	14	4	13
RR[b]	0.24	1.00	0.53	0.68	0.68	0.26	0.31
	(0.18-0.33)		(0.25-1.12)	(0.35-1.34)	(0.39-1.19)	(0.10-0.65)	(0.18-0.53)
RR[c]	0.23	1.00	1.47	0.58	0.72	0.28	0.32
	(0.17-0.33)		(0.42-5.20)	(0.23-1.44)	(0.36-1.42)	(0.09-0.87)	(0.16-0.66)
Nonfatal Myocardial Infarction							
Cases	166	418	36	22	26	13	41
RR[b]	0.26	1.00	0.85	0.51	0.40	0.26	0.29
	(0.22-0.30)		(0.60-1.19)	(0.34-0.78)	(0.27-0.59)	(0.15-0.43)	(0.21-0.39)
RR[c]	0.24	1.00	0.81	0.43	0.38	0.26	0.27
	(0.20-0.28)		(0.51-1.29)	(0.25-0.74)	(0.23-0.62)	(0.13-0.49)	(0.18-0.41)
Total Coronary Heart Disease							
Cases	215	541	43	31	40	17	54
RR[b]	0.25	1.00	0.77	0.55	0.47	0.26	0.29
	(0.22-0.30)		(0.57-1.05)	(0.39-0.79)	(0.34-0.64)	(0.17-0.40)	(0.23-0.38)
RR[c]	0.24	1.00	0.75	0.46	0.44	0.26	0.28
	(0.20-0.28)		(0.49-1.15)	(0.29-0.74)	(0.30-0.66)	(0.14-0.45)	(0.20-0.40)

[a] *Years since quitting was missing for 29 cases, including 6 fatal coronary heart disease and 23 nonfatal myocardial infarction.*

[b] *Age-adjusted RR.*

[c] *Adjusted for age in 5-year intervals, followup period (1976 to 1978, 1978 to 1980, 1980 to 1982, 1982 to 1984, 1984 to 1986, or 1986 to 1988), history of hypertension, diabetes, high cholesterol levels, body mass index, past use of oral contraceptives, menopausal status, postmenopausal estrogen therapy, parental history of myocardial infarction before age 60, and daily number of cigarettes consumed.*

Key: RR = relative risk.

the conclusion that 10 years of cessation were required for the risk to drop to the level of never-smokers.

Age at Starting To Smoke

We analyzed, separately for former and current smokers, the relationship of age at starting smoking with the risk of CHD. Among current smokers, the risk of CHD was increased at any age of starting to smoke. However, those who started to smoke before age 15 had the highest age-adjusted relative risks for total CHD (7.17, 95-percent CI: 4.88-10.53) (Table 13). After adjusting for potential confounding factors, including daily number of cigarettes smoked, the relative risk for those starting to smoke before age 15 increased to 9.25 (95-percent CI: 5.27-16.23). The confidence interval of this estimate excluded those of other categories of age at starting.

Table 13
Age at starting to smoke among current and former smokers and age-adjusted and multivariate RR's of total coronary heart disease, compared with never-smokers

		Age at Starting To Smoke[a]				
Event	Never-Smoker	<15 Years	15-17	18-21	22-25	≥26 Years
Total Coronary Heart Disease—Former Smokers						
Cases	215	4	25	140	28	12
RR[b]	1.00	1.72 (0.65-4.58)	1.35 (0.89-2.03)	1.57 (1.27-1.94)	1.44 (0.97-2.13)	1.34 (0.75-2.39)
RR[c]	1.00	7.55 (2.54-22.45)	1.42 (0.84-2.40)	1.66 (1.28-2.16)	1.83 (1.12-2.98)	1.67 (0.83-3.36)
Total Coronary Heart Disease—Current Smokers						
Cases	215	21	66	336	73	40
RR[b]	1.00	7.17 (4.88-10.53)	3.21 (2.47-4.17)	4.17 (3.55-4.89)	3.91 (3.06-5.00)	3.19 (2.32-4.40)
RR[d]	1.00	9.25 (5.27-16.23)	3.41 (2.38-4.89)	4.53 (3.59-5.71)	4.30 (3.03-6.12)	3.17 (2.10-4.78)

[a] Age at starting smoking was missing for five current smokers and five former smokers.
[b] Age-adjusted RR.
[c] Adjusted for coronary heart disease risk factors, plus time since quitting smoking.
[d] Adjusted for age in 5-year intervals, followup period (1976 to 1978, 1978 to 1980, 1980 to 1982, 1982 to 1984, 1984 to 1986, or 1986 to 1988), history of hypertension, diabetes, high cholesterol levels, body mass index, past use of oral contraceptives, postmenopausal estrogen therapy, and daily number of cigarettes consumed.

Key: RR = relative risk.

Among former smokers, women who started before age 15 were also at highest risk of total CHD, although this finding was based on only a few cases (n = 4) (Table 13). After adjusting for potential confounding factors (including CHD risk factors, daily number of cigarettes smoked, and years since stopping), the relative risk of former smokers who started before age 15 was 7.55 (95-percent CI:2.54-22.45).

DISCUSSION

Total Mortality

Studies of cigarette smoking carried out among women during the 1950's and 1960's reported relative risks of total mortality ranging between 1.3 and 1.4 (Doll and Hill, 1956; Hammond and Horn, 1958; Dunn et al., 1960; Best et al., 1961; Kahn, 1966; Hammond, 1966), whereas smokers in the Nurses' Health Study (Colditz, 1990) were at nearly 1.9 times the risk compared with never-smokers (Table 2). This may be explained partly by the fact that that study represents a younger age cohort, one likely to have higher relative risks. In addition, the higher relative risk estimates may be attributable to the increasing proportion of women in more recent birth cohorts who are heavier smokers and who started smoking at a young age. Data from National Health Interview Surveys indicate that the proportion of women starting to smoke before the age of 16 increased from 7.2 percent among women born from 1910 to 1914

to 20.2 percent among those born between 1950 and 1954 (U.S. Department of Health and Human Services, 1989). In the Nurses' Health Study (Colditz, 1990), women who started smoking before age 15 had the highest risk (multivariate RR = 3.15) of total mortality (Table 4). Furthermore, the observed deaths in this study were premature because they all occurred among women who were younger than 67 years of age during the 12 years of followup. A recent study of smoking-attributable deaths in developed countries estimated that those killed by tobacco between ages 35 and 69 lose an average of about 23 years of life (Peto et al., 1992).

The time required for the risk of total mortality among quitters to reach the level of never-smokers differs across studies. The Nurses' Health Study (Colditz, 1990) data indicate that the risk among former smokers declines to the level of never-smokers 10 to 14 years after cessation. This estimate of the time required is somewhat shorter than that of several of the previous studies. For example, the American Cancer Society Cancer Prevention Study I (ACS CPS-I) found that among former smokers of 20 or more cigarettes per day, risk of total mortality was still higher than that of never-smokers even 10 years after cessation (Hammond, 1966). In the more recent ACS CPS-II study, involving 4 years of followup among 521,555 men and 658,748 women, the risk of total mortality among female former smokers declined to the level of never-smokers 16 or more years after cessation (U.S. Department of Health and Human Services, 1990). Also, in the U.S. Veterans Study (Rogot and Murray, 1980), the overall mortality risk among male smokers remained elevated 15 or more years after cessation (RR = 1.47 among smokers of 10 to 20 cigarettes per day; RR = 1.22 among smokers of 21 to 39 cigarettes per day).

The differences among studies in estimates of the duration needed for a former smoker to have the same overall mortality risk as a never-smoker may be due partly to factors such as the lack of ascertainment of smoking status after enrollment in earlier studies (Hammond, 1966; U.S. Department of Health and Human Services, 1990; Rogot and Murray, 1980). In these studies, persons who smoked at enrollment but subsequently quit remained assigned to the current smoker category. This misclassification tends to obscure the benefits of cessation in comparison with continued smoking (U.S. Department of Health and Human Services, 1990). In contrast, the Established Populations for Epidemiologic Studies of the Elderly (EPESE) study (LaCroix et al., 1991), which updated smoking status at yearly intervals, reported that the relative risk of total mortality among formerly smoking women returned to the level of never-smokers 6 to 10 years after cessation.

A potential limitation of the present study is that our cohort consists of predominantly white middle-aged women selected with respect to a particular occupation (nursing). Although our findings might not be generalizable to older women or other ethnic groups, the qualitatively similar effects of smoking across population subgroups defined by age, gender, and race suggest that the biological effects of smoking cessation

are also not likely to differ in major ways across demographic groups. Smokers who quit may be unrepresentative in ways that could not be controlled in our analysis, although we adjusted for a broad range of potential confounding variables in our multivariate analyses. Finally, during the 12-year followup period, current smokers were marginally less likely to respond compared with former smokers. This could have potentially resulted in an underestimation of the benefits of cessation. However, the difference in response rates never exceeded 0.5 percentage points, making this an unlikely source of major bias.

The observation of an excess cancer mortality risk within the first 2 years of giving up smoking in the present study (Table 3) and in previous studies (U.S. Department of Health and Human Services, 1990) has been attributed to the ill-quitter effect. When analyses excluded women with CVD and cancer at the beginning of each 2-year followup interval, the excess risk among recent quitters was removed. The results in Tables 5 and 6 provide a comparison between the impact of stopping smoking before developing disease and the situation in which a proportion of smokers stop after the onset of disease. The benefits of smoking cessation, in terms of a reduction in all-cause as well as cause-specific mortality, occur sooner in the former case. If one stops smoking before the onset of disease, one will experience a 24-percent reduction in the risk of total mortality within 2 years of quitting (including a 37-percent reduction in CVD mortality) as well as rapid return of the risk of cancer mortality to the level of a never-smoker (Table 6). These benefits are more substantial and occur sooner than in the case of delaying the cessation of smoking until the onset of disease (Table 3).

The finding of an association between cigarette smoking and suicides/accidents has been reported in previous studies, including the British Male Doctors Study (Doll and Peto, 1976) and the Multiple Risk Factor Intervention Trial (MRFIT) study (Smith et al., 1992). Although a recent report dismissed the association as causal due to lack of biologic plausibility (Smith et al., 1992), several studies have shown an association between cigarette smoking and depression (Perez-Stable et al., 1990; Glassman et al., 1990; Anda et al., 1990; Glass, 1990). The Nurses' Health Study (Colditz, 1990) collected no data on the mental health of participants prior to 1992. On the other hand, the association between smoking and external causes of injury persisted after controlling for alcohol intake in multivariate analysis. Whether this association is causal or whether smoking is merely correlated with one or more factors (as yet unidentified) predisposing one to accidents/suicide deserves further study.

Weight gain after smoking cessation is thought to be a factor contributing to continuing smoking by women (U.S. Department of Health and Human Services, 1990). In the Nurses' Health Study (Colditz, 1990), women who quit smoking had an average 1.4 to 2.8 kg greater weight gain over an 8-year followup period compared with current smokers (Colditz et al., 1992). Our analyses of total mortality, which balance adverse as well as desirable effects of smoking cessation, clearly indicate that the health

benefits of smoking cessation far exceed the risks posed by this magnitude of weight gain (U.S. Department of Health and Human Services, 1990; Colditz et al., 1992).

The best health advice remains not to start smoking at all, particularly at a young age. However, benefits of cessation are substantial and begin to accrue almost immediately after quitting.

Stroke Incidence The Nurses' Health Study (Colditz et al., 1992) data confirm that cigarette smoking is a major contributor to the risk of ischemic and hemorrhagic stroke among women (Colditz et al., 1988; Gill et al., 1989) and that cessation leads to a decline in risk (Donnan et al., 1989; Wolf et al., 1988; Colditz et al., 1988). For total stroke, most of the benefit of stopping occurred 2 to 4 years following cessation. The relationship of time since quitting with decline in risk of total stroke was independent of amount smoked, age at starting, or the presence of other risk factors.

Our data suggest that the effect of current cigarette smoking on ischemic stroke is due predominantly to short-term effects. Consistent with this hypothesis was the lack of a relationship in the present study between the age at starting and the risk of ischemic stroke among current smokers (Table 9). The acute effects of smoking on the risk of stroke appeared to overwhelm any chronic effects, such as those mediated by atherogenesis. Once the acute insults of smoking were removed (as in the case of former smokers), the underlying relationship of age at starting smoking with risk of ischemic stroke became apparent (Table 10).

Previous studies of subarachnoid hemorrhage have reported a persistently elevated risk among former smokers (Bell and Symon, 1979; Taha et al., 1982). In the present study, the risk among former smokers appeared to return to the level of never-smokers more than 5 years after cessation. However, the number of cases on which this observation is based was small, and we cannot rule out a persisting excess risk.

Overall, the data indicate that benefits of smoking cessation in terms of stroke reduction are available to all smokers regardless of age at starting and amounts smoked. Current smokers who stop can anticipate substantial reductions in their risk of stroke within 2 to 4 years following cessation.

Coronary Heart Disease Incidence Our data confirm that cigarette smoking is a major contributor to the risk of CHD in middle-aged women (Willett et al., 1987) and that cessation leads to a decline in risk (U.S. Department of Health and Human Services, 1990). In the present study, the excess risk of total CHD among former smokers dropped by one-third within 2 years of quitting. The substantial fall in CHD risk soon after stopping was consistent with previous reports (U.S. Department of Health and Human Services, 1990; LaCroix et al., 1991; Rosenberg et al., 1985 and 1990; Dobson et al., 1991). Contrary to several earlier reports indicating a relatively short time (i.e., less than 5 years) between cessation and complete removal of risk (LaCroix et al., 1991; Rosenberg et al., 1985 and 1990; Dobson et al., 1991), we found that CHD

risk among former smokers did not decline to the level of never-smokers until 10 to 14 years after cessation.

The predominant biologic effects of smoking on CVD have been thought to be related to current use. However, both the high risk associated with early age at starting smoking and the length of time required for complete removal of risk after cessation suggest an important contribution of cumulative exposure to cigarette smoking. This pattern of decline in CHD risk contrasts with the time course of decline in stroke risk after cessation. In middle-aged women, the hazards of smoking on stroke appear to be more strongly related to current use (Colditz et al., 1988), with risk among former smokers rapidly falling to the level of never-smokers 2 to 4 years after quitting (Wolf et al., 1988; see also "Decline in Risk Among Former Smokers").

Compared with cohort studies, case-control studies (Rosenberg et al., 1985 and 1990; Dobson et al., 1991) have tended to report shorter intervals between smoking cessation and complete reversal of CHD risk. In a hospital-based case control study, Rosenberg and colleagues (1985) reported that the risk of nonfatal MI among male former smokers returned to the level of never-smokers after 23 months. In a separate study of nonfatal MI among women, Rosenberg and coworkers (1990) found that the risk among former smokers was indistinguishable from that of never-smokers 36 months after cessation. In a population-based case-control study, Dobson and colleagues (1991) found that the risk among male and female former smokers returned to the level of never-smokers 4 years after cessation.

A case-control study, based on 263 women in the Nurses' Health Study (Colditz, 1990) cohort who reported a nonfatal MI on the 1976 baseline questionnaire, found that when compared with never-smokers, those who quit 1 to 4 or 5 to 9 years earlier had a significantly elevated risk of 1.5, whereas those who had quit 10 years or more earlier had a relative risk of 0.6 (Willett et al., 1981). However, because there were only 29 cases among former smokers, the estimates of risk by duration of quitting were not precise.

In contrast to the majority of case-control studies, cohort studies have generally reported longer intervals between quitting and the decline of CHD risk among former smokers to the level of never-smokers. In their prospective study of 188,000 white men ages 50 to 69 years, Hammond and Horn (1958) stated that it took 10 years for the risk of CHD deaths among former smokers to reach that of never-smokers, provided that they had smoked less than 1 packet of cigarettes per day. If they smoked more than 1 packet per day, the relative risk was 1.6 even 10 years after cessation. In other cohort studies, the relative risk of CHD mortality among former smokers relative to never-smokers was 1.16-1.26 at 5 to 9 years after cessation in the ACS CPS-I cohort (Hammond and Garfinkel, 1969); 1.4 at 5 to 9 years after cessation in the U.S. Veterans Study (Dorn, 1959; Kahn, 1966; Rogot and Murray, 1980); 1.3-1.4 at 5 to 9 years after cessation in the British Male Doctors Study (Doll and Peto, 1976); 1.6 at 20 years after cessation in the British Regional Heart Study (Cook et al., 1986; Cook and Shaper, 1986); 1.28 at 2 to 9 years after cessation in the Coronary Artery Surgery Study

registry (Omenn et al., 1990); and 1.5 at 1 to 9 years after cessation in a Swedish cohort study (Cederlof et al., 1975). The 22-year followup report of the British Female Doctors Study (Doll et al., 1980) had insufficient data on former smokers to allow examination of CHD risk according to time since quitting.

Case-control studies have been suggested to be less susceptible to misclassification resulting from recidivism, that is, resumption of smoking among former smokers. In followup studies that measure smoking status only at entry into the study, coronary events that occur among former smokers who have resumed smoking are erroneously counted as occurring in former smokers instead of current smokers. This may result in a longer estimate of the time required for the risk to decline to the level of never-smokers (Rosenberg et al., 1985; Dobson et al., 1991). Although this type of misclassification may have occurred in cohort studies that ascertained smoking habits at baseline only (e.g., the ACS studies [Hammond, 1966; Stellman and Garfinkel, 1986; Hammond and Garfinkel, 1969], the U.S. Veterans Study [Dorn, 1959; Kahn, 1966; Rogot and Murray, 1980], and the Swedish cohort study [Cederlof et al., 1975]), in the present study smoking status was updated every 2 years. Most relapses among quitters occur within the first 2-year period after cessation (U.S. Department of Health and Human Services, 1990). Furthermore, within any 2-year followup period in the Nurses' Health Study (Colditz, 1990), an average of only 1,500 quitters (or about 4.8 percent of former smokers) resumed smoking. These numbers were too small to explain the discrepancy between previous case-control studies and the present study in the time taken for risk of CHD among former smokers to decline to the level of never-smokers.

Starting smoking before age 15 is associated with a particularly high risk of CHD. In American women, the age at initiation has been steadily falling. Data from National Health Interview Surveys indicate that the proportion of women starting to smoke before age 16 increased from 7.2 percent among women born from 1910 to 1914 to 20.2 percent among women born between 1950 and 1954 (U.S. Department of Health and Human Services, 1989). This highlights the need for public health measures to be directed especially at preventing young women from starting to smoke.

CONCLUSIONS

- Compared with never-smokers, women who currently smoke are at increased risks of total mortality (multivariate RR = 1.87, 95-percent CI: 1.65 to 2.13), total CHD incidence (multivariate RR = 4.23, 95-percent CI: 3.60 to 4.96), and total stroke incidence (multivariate RR = 2.73, 95-percent CI: 2.18 to 3.41).
- Starting smoking before age 15 is associated with particularly high risks of total mortality (multivariate RR = 3.15, 95-percent CI: 2.16 to 4.59) and total CHD incidence (multivariate RR = 9.25, 95-percent CI:5.27 to 16.23).

- Compared with never-smokers, former smokers are at slightly higher risk of total mortality (multivariate RR = 1.29, 95-percent CI: 1.14 to 1.46), total CHD incidence (multivariate RR = 1.48, 95-percent CI: 1.22 to 1.79), and total stroke incidence (multivariate RR = 1.35, 95-percent CI: 0.98 to 1.85).
- The risk of total mortality among former smokers approaches the level of never-smokers 10 to 14 years after cessation. This conclusion remained unchanged after taking account of the ill-quitter effect.
- On stopping smoking, former smokers removed one-third of the excess risk of total CHD incidence within 2 years of cessation. The risk among former smokers declines to the level of never-smokers during the interval of 10 to 14 years following cessation.
- The risk of total stroke incidence among former smokers approaches the level of never-smokers during the interval of 2 to 4 years following cessation.
- The time course of decline in risk of total mortality, total CHD incidence, and total stroke incidence remained unchanged after adjusting for age at starting smoking and number of cigarettes smoked daily.

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