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JAMA. 2008;299(17):2037-2047 (doi:10.1001/jama.299.17.2037)

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Smoking and Smoking Cessation in Relation to Mortality in Women

Stacey A. Kenfield, ScD

Meir J. Stampfer, MD, DrPH

Bernard A. Rosner, PhD

Graham A. Colditz, MD, DrPH

TOBACCO USE REMAINS THE LEADING preventable cause of death in the United States.¹ Globally, approximately 5 million premature deaths were attributable to smoking in 2000.² The World Health Organization projects by 2030 that tobacco-attributable deaths will annually account for 3 million deaths in industrialized countries and 7 million in developing countries.^{2,3} The hazards of smoking have been documented over the past 55 years, providing sufficient evidence of a causal relationship between smoking and many types of death.

After 12 years of follow-up in the Nurses' Health Study, Kawachi et al⁴ described the extent of the increase in risk of total and cause-specific mortality (vascular disease, cancer including and excluding lung cancer, and external causes of death) associated with current smoking and early age at smoking initiation compared with never smokers, as well as the decrease in risk associated with smoking cessation compared with continuing smokers. We have continued to follow up these women over time. With 22 years of follow-up, we are now able to characterize the relationship of smoking with other causes of death, including respiratory diseases and cancers.

See also Patient Page.

Context Smoking is associated with an increased risk of total and cause-specific death, but the rate of mortality risk reduction after quitting compared with continuing to smoke is uncertain. There is inadequate or insufficient evidence to infer the presence or absence of a causal relationship between smoking and ovarian cancer and colorectal cancer.

Objective To assess the relationship between cigarette smoking and smoking cessation on total and cause-specific mortality in women.

Design, Setting, and Participants Prospective observational study of 104 519 female participants in the Nurses' Health Study with follow-up from 1980 to 2004.

Main Outcome Measure Hazard ratios (HRs) for total mortality, further categorized into vascular and respiratory diseases, lung cancer, other cancers, and other causes.

Results A total of 12 483 deaths occurred in this cohort, 4485 (35.9%) among never smokers, 3602 (28.9%) among current smokers, and 4396 (35.2%) among past smokers. Compared with never smokers, current smokers had an increased risk of total mortality (HR, 2.81; 95% confidence interval [CI], 2.68-2.95) and all major cause-specific mortality. The HR for cancers classified by the 2004 surgeon general's report to be smoking-related was 7.25 (95% CI, 6.43-8.18) and 1.58 (95% CI, 1.45-1.73) for other cancers. Compared with never smokers, the HR for colorectal cancer was 1.63 (95% CI, 1.29-2.05) for current smokers and 1.23 (95% CI, 1.02-1.49) for former smokers. A significant association was not observed for ovarian cancer. Significant trends were observed for earlier age at initiation of smoking for total mortality ($P=.003$), respiratory disease mortality ($P=.001$), and all smoking-related cancer mortality ($P=.001$). The excess risk for all-cause mortality decreases to the level of a never smoker 20 years after quitting, with different time frames for risk reduction observed across outcomes. Approximately 64% of deaths among current smokers and 28% of deaths among former smokers were attributable to cigarette smoking.

Conclusions Most of the excess risk of vascular mortality due to smoking in women may be eliminated rapidly upon cessation and within 20 years for lung diseases. Postponing the age of smoking initiation reduces the risk of respiratory disease, lung cancer, and other smoking-related cancer deaths but has little effect on other cause-specific mortality. These data suggest that smoking is associated with an increased risk of colorectal cancer mortality but not ovarian cancer mortality.

JAMA. 2008;299(17):2037-2047

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METHODS

Study Participants

The Nurses' Health Study cohort was established in 1976 when 121 700 female US registered nurses aged 30 to 55 years 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.⁵ Since 1976, this information has been updated and extended on

biennial follow-up questionnaires. This study was approved by the Partners Human Research Committee

Author Affiliations: Departments of Epidemiology (Drs Kenfield and Stampfer) and Biostatistics (Dr Rosner), Harvard School of Public Health, and Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School (Drs Kenfield, Stampfer, and Rosner), Boston, Massachusetts; and Department of Surgery, Washington University School of Medicine, St Louis, Missouri (Dr Colditz).

Corresponding Author: Stacey A. Kenfield, ScD, Channing Laboratory, 181 Longwood Ave, Room 452, Boston, MA 02115 (skenfiel@hsph.harvard.edu).

(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 reclassified by smoking status (never, past, or current), by quantity of cigarettes smoked and duration among current smokers, and by time since quitting among former smokers. For the analysis on current smoking, current smokers were classified into categories of cigarettes smoked per day of 1 to 14, 15 to 24, 25 to 34, and 35 or more and categories of age at initiation of smoking of 17 years or younger, 18 to 21 years, 22 to 25 years, and 26 years or older. For the smoking cessation analysis, past smokers were classified into categories of time since quitting: less than 5 years, 5 to less than 10 years, 10 to less than 15 years, 15 to less than 20 years, and 20 or more years.

Ascertainment of Mortality

The main outcome was death from all causes, occurring after the 1980 questionnaire was returned but before June 1, 2004. Deaths were grouped into 6 broad categories: vascular diseases; respiratory diseases; lung cancer; all smoking-related cancers (cancers denoted by the 2004 surgeon general's report to be caused by smoking⁶) including those of the lip, mouth, pharynx, esophagus, larynx, pancreas, bladder and kidney, cervix, stomach, trachea and lung, and acute myeloid leukemia; other cancers; and other causes. Vascular deaths were further categorized into deaths due

to coronary heart disease and cerebrovascular disease. Respiratory deaths were further categorized into those due to chronic obstructive pulmonary disease (COPD), as well as a broader category that included COPD as well as nonspecified diseases of the respiratory system (this grouping may include some participants with COPD who were not diagnosed).

Deaths were usually reported by families, and deaths among nonrespondents were identified by searching the National Death Index.⁷ The cause of death was ascertained and the pertinent medical records were obtained. Study physicians reviewed these records and the death certificate to classify individual causes of death. Cause of death was based on death certificate information only for 6.1% of deaths.

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 (June 1, 2004), whichever came first. We started follow-up in 1980 because alcohol use and physical activity were not ascertained until this follow-up cycle. Person-time for each 2-year follow-up period was equal to the number of months between the return of successive questionnaires. Women did not contribute person-time in follow-up cycles in which they were missing smoking data.

We evaluated the effect of cigarettes smoked per day, age at starting smoking, and time since quitting smoking on total and cause-specific mortality. We decided not to present data on pack-years because this variable combines cigarettes smoked per day and duration of smoking. This results in women with widely different doses and durations being classified as having the same pack-years exposure, and may misrepresent the 2 terms included in this summary measure.⁸ (The findings for pack-years of smoking in relation to mortality are available from the authors on request.) We chose to evalu-

ate cancers not classified by the 2004 surgeon general's report to be smoking-related if more than 300 cancer-specific deaths were available. Lastly, we evaluated birth cohort effects in our population by evaluating the hazard ratios (HRs) for those born between 1920-1929 and 1930-1939, excluding deaths before age 56 years. We used never smokers as the reference group for the analyses evaluating the HRs for cigarettes smoked per day and age at initiation among current smokers, and current smokers as the reference group for the analysis evaluating the HRs for time since quitting among former smokers.⁹

For all analyses, we used Cox proportional hazard models conditioned on age in months and follow-up cycle. All multivariate models included history of hypertension, diabetes, and high cholesterol levels, body mass index calculated as weight in kilograms divided by height in meters squared, change in weight from age 18 years to baseline, alcohol intake (categories of nondrinkers and drinkers of 0.1-4.9, 5.0-14.9, and ≥ 15.0 g/d), physical activity (quintiles based on intensity level and a metabolic equivalent task value calculated from the specific activity engaged in most frequently (1980-1984) and metabolic equivalent task hours per week (1986-2000), previous use of oral contraceptives (never, past, or current), postmenopausal estrogen therapy use (never, past, or current) and menopausal status, and parental history of myocardial infarction at age 65 years or younger. We also adjusted for servings of beef, pork, lamb, or processed meat, total calcium and folate intake, and duration of aspirin use when evaluating the relationship between smoking and colorectal cancer mortality. All variables except height were updated biennially until diagnosis of a nonfatal disease.

Tests for linear trend were calculated, using the Wald test, excluding the reference category and using the midpoint of the categories for cigarettes smoked per day and years since quitting, and the reported age at which the

participant started smoking. The exposed attributable fraction was calculated using the HRs for current or former smokers compared with never smokers.

For all analyses, we excluded participants with a prior history of cancer (other than non-melanoma skin cancer), vascular disease, or respiratory disease before baseline. We also excluded those participants ($n=1872$) who had smoked but did not provide their age at smoking initiation. There were 104 519 participants included in the analyses of number of cigarettes smoked per day and smoking cessation, and 79 172 participants included in the analyses of age at initiation of smoking because this analysis included only current and never smokers. All analyses were conducted using SAS software version 9 (SAS Institute Inc, Cary, North Carolina). All P values were based on 2-sided tests and were considered statistically significant at $P \leq .05$.

Confounding by Intermediate Variables

Nonfatal diseases that occur during follow-up may affect subsequent smoking and act as an intermediate variable between smoking and mortality. For example, a person experiencing a nonfatal myocardial infarction may reduce their smoking or quit smoking altogether,^{9,10} and this myocardial infarction (partly induced by smoking) may increase her risk of death. The extent of this type of confounding was evaluated in the first report on smoking and coronary heart disease mortality by performing the G-computational algorithm,^{11,12} and the risk estimates were identical to the crude estimates of risk. In the analyses presented herein, we attempted to address the problem of confounding by nonfatal diseases by stopping the updating of smoking and all covariates for those participants developing any of the following nonfatal diseases: vascular disease, cancer, or respiratory disease. We used the covariate information provided in the period prior to

Table 1. Age-Standardized Characteristics by Smoking Status of 104 519 Women in the Nurses' Health Study at Baseline in 1980^a

Characteristic	Smoking Status		
	Never	Past	Current
Smoking status of participants, %	45.7	26.0	28.3
Total person-years of follow-up (1980-2004) ^b	1.1 million	802 943	420 761
Duration of smoking, mean (SD), y	NA	15.0 (0.03)	26.5 (0.03)
Age at smoking initiation, mean (SD), y	NA	19.7 (0.02)	19.9 (0.02)
Body mass index, mean (SD) ^c	24.7 (0.02)	24.6 (0.03)	23.8 (0.03)
Weight increase since age 18 y, mean (SD), kg	21.2 (0.12)	19.1 (0.15)	13.0 (0.15)
Hypertension, %	5.6	5.8	5.1
Diabetes, %	0.7	0.6	0.7
High cholesterol, %	1.8	2.1	2.0
Parental MI at age ≤ 65 y, %	18.8	21.0	21.6
Postmenopausal hormone use, %	13.0	14.3	15.7
Alcohol intake ≥ 15 g/d, %	4.9	11.6	13.8
Vigorous exercise ≥ 1 /wk with activity ≥ 4 METs, %	25.1	29.2	22.1
Oral contraceptive use, %	39.9	43.7	43.8

Abbreviations: MET, metabolic equivalent task; MI, myocardial infarction; NA, data not applicable.

^aA supplemental table analyzed by pack-years of smoking is available from the authors on request.

^bActual years, not age-standardized.

^cCalculated as weight in kilograms divided by height in meters squared.

diagnosis of the nonfatal disease in all subsequent follow-up periods for these participants.

RESULTS

A total of 12 483 deaths occurred in this cohort, 4485 (35.9%) among never smokers, 3602 (28.9%) among current smokers, and 4396 (35.2%) among past smokers. There were 2957 vascular deaths with 1385 deaths due to coronary heart disease and 734 due to cerebrovascular disease, 759 respiratory deaths with 163 due to COPD, 1237 lung cancer deaths, 2104 smoking-related cancer deaths (including lung cancer), 3805 deaths due to other cancers, and 2858 deaths due to other causes. Age-standardized characteristics at baseline are presented by smoking status (TABLE 1). In 1980, 28% of participants were current smokers, 26% were past smokers, and 46% were never smokers. In 2002, only 8% of those alive were current smokers. Current smokers had less increase in weight since age 18 years, slightly less hypertension and a lower body mass index, more alcohol use (≥ 15 g/d), and less vigorous weekly exercise than former or never smokers.

Current Smokers

Compared with never smokers, current smokers had an increased risk of dying from any major cause during follow-up (TABLE 2). Risks increased significantly with number of cigarettes smoked per day for all major causes (except for cerebrovascular deaths; P for trend = .08). The strongest associations for the category of 35 or more cigarettes smoked per day were for COPD (HR, 114.55; 95% confidence interval [CI], 42.81-306.54) and lung cancer (HR, 39.88; 95% CI, 30.14-52.78). Multivariate-adjusted risk estimates for current smoking for cancers included in the all smoking-related cancers group (in addition to lung cancer) are as follows: acute myeloid leukemia ($n=202$; HR, 1.72 [95% CI, 1.15-2.58]); bladder and kidney ($n=184$; HR, 2.97 [95% CI, 2.00-4.42]); cervix ($n=29$; HR, 10.18 [95% CI, 3.46-29.93]); esophagus ($n=44$; HR, 7.03 [95% CI, 2.96-16.69]); lip and mouth ($n=30$; HR, 4.72 [95% CI, 1.84-12.13]); pharynx ($n=23$; HR, 6.01 [95% CI, 1.75-20.69]); pancreas ($n=383$; HR, 1.84 [95% CI, 1.39-2.43]); and stomach ($n=108$; HR, 1.59 [95% CI, 0.96-2.64]). Only 9 deaths were due to laryngeal cancer, and all were among current smokers.

Table 2. Total and Cause-Specific Mortality by Number of Cigarettes Smoked per Day Among 104 519 Women in the Nurses' Health Study Followed Up From 1980 to 2004^a

	Smoking Status			No. of Cigarettes/d Smoked by Current Smokers				P Value for Trend
	Never	Past	Current	1-14	15-24	25-34	≥35	
Total mortality								
Person-years of follow-up (% of women)	1.1 million (46.8)	802 943 (34.9)	420 761 (18.3)	140 765 (6.1)	172 916 (7.5)	71 045 (3.1)	36 035 (1.6)	
No. of deaths (n = 12 483)	4485	4396	3602	973	1507	701	421	
Adjusted HR (95% CI) ^b	1 [Reference]	1.23 (1.18-1.28)	2.77 (2.65-2.90)	1.98 (1.84-2.12)	2.92 (2.75-3.10)	3.67 (3.38-3.97)	4.43 (4.00-4.90)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	1.39 (1.33-1.45)	2.81 (2.68-2.95)	2.15 (2.00-2.31)	2.90 (2.73-3.08)	3.49 (3.21-3.79)	4.01 (3.62-4.44)	<.001
Total vascular disease^d								
No. of deaths (n = 2957)	1073	977	907	261	396	163	87	
Adjusted HR (95% CI) ^b	1 [Reference]	1.14 (1.04-1.24)	2.99 (2.73-3.27)	2.24 (1.95-2.56)	3.31 (2.94-3.71)	3.70 (3.13-4.37)	4.02 (3.22-5.01)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	1.32 (1.20-1.44)	3.26 (2.97-3.59)	2.66 (2.31-3.06)	3.53 (3.12-3.98)	3.73 (3.14-4.42)	3.73 (2.98-4.67)	<.001
Total coronary heart disease								
No. of deaths (n = 1385)	492	420	473	127	210	85	51	
Adjusted HR (95% CI) ^b	1 [Reference]	1.07 (0.94-1.22)	3.34 (2.94-3.80)	2.33 (1.91-2.83)	3.77 (3.20-4.44)	4.15 (3.29-5.24)	4.92 (3.67-6.58)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	1.24 (1.09-1.42)	3.91 (3.41-4.48)	3.00 (2.45-3.67)	4.36 (3.68-5.17)	4.40 (3.46-5.59)	4.67 (3.47-6.28)	<.001
Total cerebrovascular disease								
No. of deaths (n = 734)	277	244	213	61	99	35	18	
Adjusted HR (95% CI) ^b	1 [Reference]	1.11 (0.93-1.32)	2.82 (2.35-3.38)	2.11 (1.59-2.78)	3.31 (2.62-4.18)	3.14 (2.20-4.48)	3.34 (2.06-5.41)	.02
Multivariate HR (95% CI) ^c	1 [Reference]	1.27 (1.06-1.51)	2.81 (2.32-3.41)	2.27 (1.70-3.02)	3.23 (2.53-4.11)	2.94 (2.05-4.23)	2.95 (1.81-4.80)	.08
Total respiratory disease^e								
No. of deaths (n = 759)	113	306	340	68	152	71	49	
Adjusted HR (95% CI) ^b	1 [Reference]	3.34 (2.69-4.15)	11.86 (9.57-14.71)	5.88 (4.35-7.96)	13.50 (10.55-17.28)	18.54 (13.72-25.04)	27.65 (19.65-38.91)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	3.93 (3.16-4.90)	10.00 (7.98-12.53)	5.41 (3.97-7.39)	10.61 (8.21-13.72)	14.72 (10.79-20.08)	21.59 (15.22-30.63)	<.001
COPD^f								
No. of deaths (n = 163)	6	69	88	19	35	20	14	
Adjusted HR (95% CI) ^b	1 [Reference]	13.86 (6.02-31.93)	56.44 (24.64-129.28)	29.59 (11.80-74.20)	58.15 (24.40-138.56)	93.01 (37.15-232.87)	155.63 (59.23-408.95)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	15.91 (6.88-36.82)	39.63 (17.11-91.80)	23.29 (9.18-59.10)	36.56 (15.14-88.33)	61.67 (24.25-156.80)	114.55 (42.81-306.54)	<.001
COPD and nonspecified respiratory disease								
No. of deaths (n = 499)	26	196	277	55	117	62	43	
Adjusted HR (95% CI) ^b	1 [Reference]	9.34 (6.20-14.07)	43.67 (29.16-65.39)	21.29 (13.34-34.00)	47.14 (30.73-72.30)	73.70 (46.43-116.99)	113.50 (69.27-185.97)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	11.24 (7.44-16.97)	34.66 (22.94-52.37)	18.64 (11.57-30.03)	34.30 (22.16-53.10)	53.94 (33.65-86.48)	84.44 (51.00-139.80)	<.001
Lung cancer								
No. of deaths (n = 1237)	109	437	691	143	300	148	100	
Adjusted HR (95% CI) ^b	1 [Reference]	4.93 (4.00-6.08)	21.87 (17.85-26.80)	11.78 (9.17-15.12)	24.25 (19.45-30.25)	32.46 (25.27-41.68)	44.03 (33.43-57.97)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	5.35 (4.33-6.62)	21.09 (17.13-25.97)	11.99 (9.30-15.46)	22.81 (18.20-28.59)	30.31 (23.50-39.10)	39.88 (30.14-52.78)	<.001
All smoking-related cancers^g								
No. of deaths (n = 2104)	434	747	923	211	384	201	127	
Adjusted HR (95% CI) ^b	1 [Reference]	2.12 (1.88-2.39)	7.29 (6.50-8.18)	4.37 (3.70-5.15)	7.67 (6.67-8.81)	11.00 (9.29-13.03)	13.91 (11.38-17.01)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	2.33 (2.06-2.63)	7.25 (6.43-8.18)	4.59 (3.87-5.43)	7.45 (6.46-8.60)	10.53 (8.86-12.53)	12.78 (10.41-15.68)	<.001

(continued)

Table 2. Total and Cause-Specific Mortality by Number of Cigarettes Smoked per Day Among 104 519 Women in the Nurses' Health Study Followed Up From 1980 to 2004^a (cont)

	Smoking Status			No. of Cigarettes/d Smoked by Current Smokers				P Value for Trend
	Never	Past	Current	1-14	15-24	25-34	≥35	
Other cancers^h								
No. of deaths (n = 3805)	1648	1337	820	250	332	158	80	
Adjusted HR (95% CI) ^b	1 [Reference]	1.02 (0.95-1.10)	1.57 (1.44-1.71)	1.30 (1.14-1.49)	1.59 (1.41-1.79)	1.97 (1.67-2.32)	2.00 (1.59-2.50)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	1.09 (1.01-1.18)	1.58 (1.45-1.73)	1.37 (1.20-1.57)	1.59 (1.41-1.79)	1.89 (1.60-2.23)	1.83 (1.46-2.29)	<.001
Colorectal cancer								
No. of deaths (n = 578)	238	214	126	36	55	28	7	
Adjusted HR (95% CI) ^b	1 [Reference]	1.13 (0.94-1.36)	1.69 (1.36-2.10)	1.32 (0.93-1.87)	1.83 (1.36-2.46)	2.05 (1.43-2.94) ⁱ		.02
Multivariate HR (95% CI) ^{c,j}	1 [Reference]	1.23 (1.02-1.49)	1.63 (1.29-2.05)	1.37 (0.95-1.96)	1.73 (1.27-2.35)	1.83 (1.26-2.64) ⁱ		.23
Ovarian cancer								
No. of deaths (n = 467)	214	167	86	27	40	15	4	
Adjusted HR (95% CI) ^b	1 [Reference]	0.98 (0.80-1.20)	1.21 (0.94-1.56)	1.05 (0.71-1.58)	1.39 (0.99-1.96)	1.15 (0.71-1.84) ⁱ		.82
Multivariate HR (95% CI) ^c	1 [Reference]	1.03 (0.83-1.27)	1.20 (0.92-1.56)	1.07 (0.71-1.62)	1.36 (0.96-1.93)	1.09 (0.68-1.76) ⁱ		.96
Other causes								
No. of deaths (n = 2858)	1217	1029	612	183	243	108	78	
Adjusted HR (95% CI) ^b	1 [Reference]	1.11 (1.02-1.21)	1.82 (1.65-2.01)	1.46 (1.25-1.71)	1.82 (1.58-2.09)	2.15 (1.76-2.62)	2.95 (2.34-3.72)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	1.26 (1.15-1.37)	1.87 (1.68-2.07)	1.61 (1.37-1.89)	1.83 (1.59-2.12)	2.04 (1.67-2.50)	2.76 (2.18-3.50)	<.001

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio.

^aAll covariates including smoking updated until diagnosis of disease.

^bAge-adjusted relative risk.

^cAdjusted for age (months), follow-up period, history of hypertension, diabetes, high cholesterol levels, body mass index, change in weight from age 18 years to baseline (1980), alcohol intake, physical activity, previous use of oral contraceptives, postmenopausal estrogen therapy use and menopausal status, parental history of myocardial infarction at age 65 years or younger, and age at starting smoking.

^dIncludes coronary heart disease and cerebrovascular disease.

^eIncludes COPD and excludes lung cancer.

^fIncludes chronic bronchitis and emphysema.

^gAccording to the 2004 Surgeon General's report, includes acute myeloid leukemia, bladder, cervical, esophageal, kidney, larynx, oral cavity and pharynx, pancreas, stomach, and trachea or lung.

^hAll cancers not confirmed by the 2004 Surgeon General's report to be smoking-related cancers: colorectal, ovarian, etc.

ⁱCategories were collapsed due to the limited number of cases.

^jIn addition to adjusting for the covariates in footnote c, adjusted for servings of beef, pork, lamb, or processed meat, total calcium and folate intake, and duration of aspirin use.

For the relationship between smoking and cancer mortality, sites with more than 300 cancer-specific deaths and sites not previously studied were explored in this cohort. There were 578 colorectal cancer deaths, 467 ovarian cancer deaths, and 1138 breast cancer deaths; however, a recent Nurses' Health Study analysis found no relationship between current smoking and breast cancer survival among those with breast cancer (relative risk, 1.00; 95% CI, 0.83-1.19).¹³ Current smokers had an increased risk of colorectal cancer mortality (HR, 1.63; 95% CI, 1.29-2.05) and a slightly elevated risk of ovarian cancer (HR, 1.20; 95% CI, 0.92-1.56) compared

with never smokers, but a significant trend for cigarettes smoked per day for colorectal and ovarian cancer mortality was not observed. Overall, approximately 64% of all deaths among current smokers were attributable to cigarette smoking; specifically, 69% of vascular deaths, 90% of respiratory deaths, 95% of lung cancer deaths, 86% of lung and other smoking-related cancer deaths, 37% of other cancer deaths, and 47% of other deaths were attributable to current cigarette smoking.

The HR for total mortality for current smokers who started smoking at age 17 years or younger was 2.93 (95% CI, 2.70-3.18), 22% higher than

for those starting at or after 26 years (HR, 2.40 [95% CI, 2.08-2.78]; TABLE 3). For vascular disease and its subgroups, the HRs for age at starting smoking did not change significantly with increasing age ($P = .84$), while a significant downward trend was observed with increasing age for respiratory disease ($P = .001$), lung cancer ($P < .001$), and smoking-related cancer mortality ($P = .001$).

The hazards for total mortality in both birth cohorts were similar but because the mean age at smoking initiation was 19.9 years for those born in the 1920s and 19.3 years for those born in the 1930s, we did not expect to observe differences by birth cohort.

Former Smokers

We observed a significant 13% reduction in the risk of all-cause mortality within the first 5 years of quitting smoking compared with continuing to smoke, and the excess risk decreased

to the level of a never smoker 20 years after quitting (TABLE 4 and FIGURE), with some causes taking more or less time. Significant trends were observed with increasing years since quitting for all major cause-specific

outcomes. A more rapid decline in risk after quitting smoking compared with continuing to smoke was observed in the first 5 years for vascular diseases compared with other causes. Much of the reduction in the

Table 3. Total and Cause-Specific Mortality by Age at Starting Smoking Among 79 172 Current Smokers in the Nurses' Health Study Followed Up From 1980 to 2004^a

	Never Smoker	Among Current Smokers, Starting Age, y				P Value for Trend
		≤17	18-21	22-25	≥26	
Total mortality						
Person-years of follow-up (% of women)	1.1 million (71.9)	92 386 (6.2)	262 856 (17.6)	43 366 (2.9)	22 152 (1.5)	
No. of deaths (n = 8087)	4485	746	2194	463	199	
Adjusted HR (95% CI) ^b	1 [Reference]	3.00 (2.78-3.25)	2.75 (2.61-2.90)	2.70 (2.45-2.98)	2.30 (1.99-2.65)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	2.93 (2.70-3.18)	2.83 (2.67-2.99)	2.79 (2.52-3.07)	2.40 (2.08-2.78)	.003
Total vascular disease^d						
No. of deaths (n = 1980)	1073	190	517	133	67	
Adjusted HR (95% CI) ^b	1 [Reference]	3.40 (2.91-3.98)	2.80 (2.51-3.11)	3.11 (2.59-3.73)	3.09 (2.41-3.97)	.56
Multivariate HR (95% CI) ^c	1 [Reference]	3.61 (3.06-4.24)	3.15 (2.82-3.53)	3.49 (2.90-4.21)	3.44 (2.67-4.42)	.84
Total coronary heart disease						
No. of deaths (n = 965)	492	101	262	76	34	
Adjusted HR (95% CI) ^b	1 [Reference]	4.02 (3.23-5.00)	3.09 (2.65-3.60)	3.79 (2.97-4.84)	3.43 (2.41-4.87)	.50
Multivariate HR (95% CI) ^c	1 [Reference]	4.53 (3.61-5.69)	3.74 (3.18-4.39)	4.59 (3.57-5.90)	3.86 (2.70-5.51)	.67
Total cerebrovascular disease						
No. of deaths (n = 490)	277	41	126	29	17	
Adjusted HR (95% CI) ^b	1 [Reference]	2.79 (2.00-3.89)	2.64 (2.13-3.27)	2.66 (1.80-3.92)	3.08 (1.87-5.06)	>.99
Multivariate HR (95% CI) ^c	1 [Reference]	2.72 (1.92-3.83)	2.65 (2.11-3.33)	2.70 (1.82-4.02)	3.14 (1.90-5.18)	.63
Total respiratory disease^e						
No. of deaths (n = 453)	113	83	203	40	14	
Adjusted HR (95% CI) ^b	1 [Reference]	17.31 (12.94-23.14)	12.15 (9.61-15.35)	9.68 (6.70-14.01)	7.32 (4.18-12.83)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	13.36 (9.78-18.25)	10.23 (7.95-13.17)	8.11 (5.54-11.87)	6.97 (3.91-12.41)	.001
COPD^f						
No. of deaths (n = 94)	6	21	57	7	3	
Adjusted HR (95% CI) ^b	1 [Reference]	74.88 (30.01-186.86)	67.61 (29.05-157.36)	29.50 (10.65-81.65) ^g		.01
Multivariate HR (95% CI) ^c	1 [Reference]	44.64 (17.25-115.52)	46.31 (19.33-110.92)	24.32 (8.60-68.83) ^g		.06
COPD and nonspecified respiratory disease						
No. of deaths (n = 303)	26	70	165	30	12	
Adjusted HR (95% CI) ^b	1 [Reference]	69.93 (43.00-111.16)	46.84 (30.67-71.51)	32.28 (18.80-55.41)	27.64 (13.78-55.40)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	51.15 (31.42-83.27)	37.69 (24.24-58.61)	26.13 (14.98-45.56)	24.43 (11.88-50.23)	<.001
Lung cancer						
No. of deaths (n = 800)	109	139	443	91	18	
Adjusted HR (95% CI) ^b	1 [Reference]	22.77 (17.65-29.36)	22.96 (18.57-28.37)	20.84 (15.72-27.63)	8.53 (5.16-14.09)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	20.80 (15.99-27.07)	22.12 (17.77-27.54)	20.23 (15.19-26.94)	8.87 (5.35-14.71)	<.001
All smoking-related cancers^h						
No. of deaths (n = 1357)	434	195	578	119	31	
Adjusted HR (95% CI) ^b	1 [Reference]	7.97 (6.71-9.47)	7.46 (6.57-8.47)	7.01 (5.71-8.61)	3.77 (2.61-5.44)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	7.34 (6.13-8.79)	7.33 (6.41-8.39)	6.97 (5.66-8.60)	3.90 (2.69-5.64)	.001
Other cancersⁱ						
No. of deaths (n = 2468)	1648	151	517	104	48	
Adjusted HR (95% CI) ^b	1 [Reference]	1.47 (1.24-1.73)	1.60 (1.45-1.77)	1.60 (1.31-1.95)	1.47 (1.10-1.97)	.69
Multivariate HR (95% CI) ^c	1 [Reference]	1.45 (1.22-1.73)	1.64 (1.48-1.83)	1.64 (1.34-2.01)	1.50 (1.13-2.01)	.93
Colorectal cancer						
No. of deaths (n = 364)	238	19	83	16	8	
Adjusted HR (95% CI) ^b	1 [Reference]	1.00 (0.55-1.79)	1.37 (0.90-2.08)		1.27 (0.75-2.15) ^g	.92
Multivariate HR (95% CI) ^{c,j}	1 [Reference]	1.25 (0.77-2.02)	1.73 (1.32-2.27)		1.55 (1.01-2.39) ^g	.95

(continued)

Table 3. Total and Cause-Specific Mortality by Age at Starting Smoking Among 79 172 Current Smokers in the Nurses' Health Study Followed Up From 1980 to 2004^a (cont)

	Never Smoker	Among Current Smokers, Starting Age, y				P Value for Trend
		≤17	18-21	22-25	≥26	
Ovarian cancer						
No. of deaths (n=300)	214	11	60	8	7	
Adjusted HR (95% CI) ^b	1 [Reference]	0.72 (0.35-1.52)	1.28 (0.78-2.08)		1.13 (0.60-2.15) ^g	.98
Multivariate HR (95% CI) ^c	1 [Reference]	0.76 (0.41-1.41)	1.36 (1.00-1.84)		1.20 (0.70-2.05) ^g	.89
Other causes						
No. of deaths (n = 1829)	1217	127	379	67	39	
Adjusted HR (95% CI) ^b	1 [Reference]	1.93 (1.60-2.33)	1.81 (1.61-2.03)	1.54 (1.20-1.97)	1.75 (1.26-2.42)	.32
Multivariate HR (95% CI) ^c	1 [Reference]	1.93 (1.59-2.34)	1.88 (1.66-2.13)	1.64 (1.27-2.11)	1.86 (1.35-2.58)	.48

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio.

^aAll covariates including smoking updated until diagnosis of disease.

^bAge-adjusted relative risk.

^cAdjusted for age (months), follow-up period, history of hypertension, diabetes, high cholesterol levels, body mass index, change in weight from age 18 years to baseline (1980), alcohol intake, physical activity, previous use of oral contraceptives, postmenopausal estrogen therapy use and menopausal status, parental history of myocardial infarction at age 65 years or younger, and daily number of cigarettes smoked. Multivariate HRs shown reflect the hazard for current smokers smoking a pack of cigarettes (20 cigarettes) per day compared with the hazard for a never smoker.

^dIncludes coronary heart disease and cerebrovascular disease.

^eIncludes COPD and excludes lung cancer.

^fIncludes chronic bronchitis and emphysema.

^gCategories were collapsed due to the limited number of cases.

^hAccording to the 2004 Surgeon General's report, includes acute myeloid leukemia, bladder, cervical, esophageal, kidney, larynx, oral cavity and pharynx, pancreas, stomach, and trachea or lung.

ⁱAll cancers not confirmed by the 2004 Surgeon General's report to be smoking-related cancers: colorectal, breast, ovarian, etc.

^jIn addition to adjusting for the covariates in footnote c, adjusted for servings of beef, pork, lamb, or processed meat, total calcium and folate intake, and duration of aspirin use.

excess risk for these causes of death were realized within the first 5 years for coronary heart disease and cerebrovascular disease. Sixty-one percent of the full potential benefit of quitting in regard to coronary heart disease mortality and 42% of the full potential benefit of quitting in regard to cerebrovascular mortality was realized within the first 5 years of quitting smoking, when comparing HRs for recent quitters of less than 5 years with long-term quitters of 20 years or greater. For death due to respiratory disease, an 18% reduction in risk of death was observed 5 to 10 years after quitting smoking, with the risk reaching that of a never smoker's risk after 20 years. This time frame for risk reduction was similar to that observed for COPD. For lung cancer mortality, a significant 21% reduction in risk was observed within the first 5 years compared with continuing smokers, but the excess risk did not disappear for 30 years. Past smokers with 20 to less than 30 years of cessation had an 87% reduction in risk of lung cancer mortality compared with current smokers (HR, 0.13; 95% CI, 0.10-

0.18) while those with 30 or more years of cessation had a 93% reduction in risk (HR, 0.07; 95% CI, 0.05-0.10). When including the other smoking-related cancers, the excess risk approached a never smoker's risk more than 20 years after quitting smoking. Although the test for trend was not significant, quitting for more than 20 years was associated with a significant 30% reduction in colorectal cancer mortality (HR, 0.70; 95% CI, 0.53-0.93) compared with continuing to smoke. Approximately 28% of all deaths among past smokers were attributable to cigarette smoking; specifically, 24% of vascular deaths, 75% of respiratory deaths, 81% of lung cancer deaths, 57% of lung and other smoking-related cancer deaths, 8% of other cancer deaths, and 21% of other deaths were attributable to former cigarette smoking.

COMMENT

This report adds to the growing evidence on the relationship between smoking and mortality.^{14,15} The original report from the Nurses' Health Study on smoking and cause-specific

mortality included 2847 deaths and evaluated the 5 mortality-specific outcomes: total mortality, total cardiovascular diseases, total cancer including and excluding lung cancer, and external causes of injury. This updated report on smoking and mortality in the Nurses' Health Study cohort includes an additional 16 years of follow-up, 12 483 deaths, and new estimates for coronary heart disease, cerebrovascular disease, respiratory disease, COPD, lung cancer, smoking-related cancers, colorectal cancer, ovarian cancer, and other causes. Because smoking behavior changes over time, updating participants' smoking status every 2 years enables more accurate evaluation of the detrimental effects from long-term smoking and the risk reduction over time from sustained cessation. The 9636 additional deaths that have accrued over time also allow for better precision in estimating the extent of risks associated with smoking and smoking cessation on causes of death previously studied.

As expected, smoking was associated with an increased risk of cause-specific mortality, with HRs 8 to 14 times higher for lung cancer mortality

Table 4. Total and Cause-Specific Mortality by Time Since Quitting Smoking Among 104 519 Women in the Nurses' Health Study Followed Up From 1980 to 2004^a

	Current Smoker	Never Smoker	Among Former Smokers, Years Since Quitting					P Value for Trend
			<5	5-<10	10-<15	15-<20	≥20	
Total mortality								
Person-years of follow-up (% of women)	420 761 (18.3)	1.1 million (46.8)	124 095 (5.4)	113 056 (4.9)	111 701 (4.9)	117 914 (5.1)	336 177 (14.6)	
No. of deaths (n = 12 483)	3602	4485	889	669	590	541	1707	
Adjusted HR (95% CI) ^b	1 [Reference]	0.36 (0.35-0.38)	0.74 (0.69-0.80)	0.55 (0.51-0.60)	0.49 (0.45-0.53)	0.43 (0.39-0.47)	0.34 (0.32-0.36)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	0.36 (0.34-0.37)	0.87 (0.81-0.94)	0.67 (0.62-0.73)	0.59 (0.54-0.65)	0.49 (0.45-0.54)	0.37 (0.35-0.39)	<.001
Total vascular disease^d								
No. of deaths (n = 2957)	907	1073	193	141	139	128	376	
Adjusted HR (95% CI) ^b	1 [Reference]	0.33 (0.31-0.37)	0.63 (0.54-0.74)	0.45 (0.38-0.54)	0.45 (0.38-0.54)	0.39 (0.33-0.47)	0.28 (0.25-0.32)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	0.31 (0.28-0.34)	0.69 (0.59-0.81)	0.52 (0.43-0.62)	0.51 (0.43-0.61)	0.43 (0.35-0.51)	0.30 (0.26-0.34)	<.001
Total coronary heart disease								
No. of deaths (n = 1385)	473	492	81	59	64	59	157	
Adjusted HR (95% CI) ^b	1 [Reference]	0.30 (0.26-0.34)	0.50 (0.40-0.64)	0.37 (0.28-0.48)	0.40 (0.31-0.53)	0.36 (0.28-0.48)	0.23 (0.19-0.28)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	0.26 (0.22-0.29)	0.53 (0.41-0.67)	0.40 (0.30-0.52)	0.43 (0.33-0.56)	0.36 (0.27-0.47)	0.23 (0.19-0.28)	<.001
Total cerebrovascular disease								
No. of deaths (n = 734)	213	277	45	30	31	35	103	
Adjusted HR (95% CI) ^b	1 [Reference]	0.36 (0.30-0.43)	0.63 (0.45-0.87)	0.41 (0.28-0.60)	0.42 (0.28-0.61)	0.44 (0.31-0.63)	0.32 (0.25-0.41)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	0.36 (0.29-0.43)	0.73 (0.53-1.01)	0.50 (0.34-0.74)	0.51 (0.35-0.74)	0.52 (0.36-0.74)	0.36 (0.28-0.46)	<.001
Total respiratory disease^e								
No. of deaths (n = 759)	340	113	98	63	47	32	66	
Adjusted HR (95% CI) ^b	1 [Reference]	0.08 (0.07-0.10)	0.86 (0.69-1.08)	0.51 (0.39-0.67)	0.37 (0.27-0.50)	0.23 (0.16-0.33)	0.11 (0.08-0.14)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	0.10 (0.08-0.13)	1.26 (1.00-1.59)	0.82 (0.62-1.07)	0.59 (0.43-0.81)	0.35 (0.24-0.51)	0.15 (0.11-0.19)	<.001
COPD^f								
No. of deaths (n = 163)	88	6	32	15	9	9	4	
Adjusted HR (95% CI) ^b	1 [Reference]	0.02 (0.01-0.04)	1.11 (0.74-1.68)	0.48 (0.28-0.84)	0.27 (0.14-0.54)	0.25 (0.12-0.49)	0.03 (0.01-0.07)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	0.03 (0.01-0.06)	1.73 (1.13-2.66)	0.87 (0.49-1.53)	0.46 (0.23-0.92)	0.44 (0.22-0.89)	0.04 (0.01-0.11)	<.001
COPD and nonspecified respiratory disease								
No. of deaths (n = 499)	277	26	76	45	30	21	24	
Adjusted HR (95% CI) ^b	1 [Reference]	0.02 (0.015-0.03)	0.81 (0.63-1.05)	0.43 (0.31-0.59)	0.27 (0.19-0.40)	0.18 (0.12-0.28)	0.05 (0.03-0.07)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	0.03 (0.02-0.04)	1.26 (0.97-1.64)	0.76 (0.55-1.05)	0.48 (0.32-0.70)	0.31 (0.20-0.49)	0.07 (0.04-0.10)	<.001
Lung cancer								
No. of deaths (n = 1237)	691	109	146	103	64	36	88	
Adjusted HR (95% CI) ^b	1 [Reference]	0.05 (0.04-0.06)	0.64 (0.53-0.76)	0.42 (0.34-0.52)	0.27 (0.21-0.35)	0.15 (0.11-0.21)	0.09 (0.07-0.11)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	0.05 (0.04-0.06)	0.79 (0.66-0.95)	0.53 (0.43-0.66)	0.33 (0.26-0.43)	0.18 (0.12-0.25)	0.10 (0.08-0.12)	<.001
All smoking-related cancers^g								
No. of deaths (n = 2104)	923	434	199	154	103	67	224	
Adjusted HR (95% CI) ^b	1 [Reference]	0.14 (0.12-0.15)	0.65 (0.56-0.76)	0.48 (0.41-0.57)	0.33 (0.27-0.41)	0.21 (0.16-0.27)	0.17 (0.14-0.19)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	0.14 (0.12-0.16)	0.79 (0.67-0.92)	0.60 (0.50-0.71)	0.40 (0.33-0.49)	0.24 (0.19-0.31)	0.19 (0.16-0.22)	<.001

(continued)

Table 4. Total and Cause-Specific Mortality by Time Since Quitting Smoking Among 104 519 Women in the Nurses' Health Study Followed Up From 1980 to 2004^a (cont)

	Current Smoker	Never Smoker	Among Former Smokers, Years Since Quitting					P Value for Trend
			<5	5-<10	10-<15	15-<20	≥20	
Other cancers^h								
No. of deaths (n = 3805)	820	1648	219	171	180	197	570	
Adjusted HR (95% CI) ^b	1 [Reference]	0.64 (0.58-0.69)	0.81 (0.70-0.94)	0.65 (0.55-0.77)	0.71 (0.60-0.83)	0.74 (0.64-0.87)	0.56 (0.50-0.63)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	0.63 (0.58-0.69)	0.89 (0.76-1.03)	0.73 (0.62-0.87)	0.79 (0.67-0.93)	0.79 (0.68-0.93)	0.61 (0.54-0.68)	<.001
Colorectal cancer								
No. of deaths (n = 578)	126	238	32	22	32	33	95	
Adjusted HR (95% CI) ^b	1 [Reference]	0.59 (0.48-0.74)	0.75 (0.51-1.11)	0.54 (0.34-0.84)	0.81 (0.55-1.20)	0.81 (0.55-1.19)	0.61 (0.46-0.79)	.41
Multivariate HR (95% CI) ^{c,i}	1 [Reference]	0.62 (0.49-0.77)	0.87 (0.59-1.29)	0.64 (0.40-1.01)	0.96 (0.65-1.43)	0.93 (0.63-1.38)	0.70 (0.53-0.93)	.40
Ovarian cancer								
No. of deaths (n = 467)	86	214	30	14	18	26	79	
Adjusted HR (95% CI) ^b	1 [Reference]	0.82 (0.64-1.06)	1.07 (0.70-1.62)	0.53 (0.30-0.94)	0.70 (0.42-1.16)	0.96 (0.62-1.49)	0.79 (0.58-1.08)	.93
Multivariate HR (95% CI) ^c	1 [Reference]	0.84 (0.64-1.09)	1.16 (0.76-1.76)	0.59 (0.33-1.04)	0.77 (0.46-1.29)	1.03 (0.66-1.61)	0.85 (0.62-1.17)	.85
Other causes								
No. of deaths (n = 2858)	612	1217	180	140	121	117	471	
Adjusted HR (95% CI) ^b	1 [Reference]	0.55 (0.50-0.61)	0.91 (0.77-1.08)	0.71 (0.59-0.86)	0.60 (0.49-0.73)	0.53 (0.44-0.65)	0.53 (0.47-0.60)	<.001
Multivariate HR (95% CI) ^c	1 [Reference]	0.54 (0.48-0.60)	1.09 (0.92-1.29)	0.87 (0.72-1.05)	0.71 (0.58-0.87)	0.61 (0.50-0.75)	0.57 (0.50-0.65)	<.001

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio.

^aAll covariates including smoking updated until diagnosis of disease.^bAge-adjusted relative risk.^cAdjusted for age (months), follow-up period, history of hypertension, diabetes, high cholesterol levels, body mass index, change in weight from age 18 years to baseline (1980), alcohol intake, physical activity, previous use of oral contraceptives, postmenopausal estrogen therapy use and menopausal status, parental history of myocardial infarction at age 65 years or younger, cigarettes smoked per day during the period prior to quitting, and age at starting smoking.^dIncludes coronary heart disease and cerebrovascular disease.^eIncludes COPD and excludes lung cancer.^fIncludes chronic bronchitis and emphysema.^gAccording to the 2004 Surgeon General's report, includes acute myeloid leukemia, bladder, cervical, esophageal, kidney, larynx, oral cavity and pharynx, pancreas, stomach, and trachea or lung.^hAll cancers not confirmed by the 2004 Surgeon General's report to be smoking-related cancers: colorectal, breast, ovarian, etc.ⁱIn addition to adjusting for the covariates in footnote c, adjusted for servings of beef, pork, lamb, processed meat, total calcium and folate intake, and duration of aspirin use.

and COPD mortality compared with total mortality. The relationship between an increasing risk of death with increasing number of cigarettes smoked per day varied by outcome. The trend was less pronounced for deaths due to vascular disease, suggesting that the first few cigarettes account for most of the increased risk; in contrast, an increase in the number of cigarettes smoked per day substantially increased the risk of death from respiratory disease.

Cohort studies consistently support an increased risk of colorectal cancer associated with current smoking, but only after accounting for an induction period of 30 to 40 years.¹⁶ Our mortality estimates are higher for current smoking and similar for former smoking compared

with estimates from the American Cancer Society Cancer Prevention Study II, which reported HRs of 1.41 (95% CI, 1.26-1.58) and 1.22 (95% CI, 1.09-1.37) for current and past smoking status, respectively, among women.¹⁷ The 2004 Surgeon General's report concluded that the evidence is suggestive but not sufficient to infer a causal relationship between smoking and colorectal cancer,⁶ mainly because of the possibility that the higher death rates from colorectal cancer may be due to less screening in smokers and a later stage of disease at diagnosis. However, we observed only modest differences in colorectal cancer screening in our cohort. In 1992, 5% of smokers reported screening by sigmoidoscopy and 31% by the stool occult

blood test in the past 2 years, vs 10% and 42%, respectively, for past smokers, and 8% and 38%, respectively, for never smokers. There was a small difference in the percentage of never smokers compared with past and current smokers who had an advanced stage of colorectal cancer at diagnosis. It is unlikely that these small differences in screening and stage at diagnosis explain the smoking and colorectal cancer mortality relationship.

The 2004 Surgeon General's report also concluded that the evidence was inadequate to infer a causal relationship between smoking and ovarian cancer.⁶ Although we observed a positive but nonsignificant relationship between current smoking and ovarian cancer mortality, we found no signifi-

cant trend with increasing cigarettes smoked per day, and age of smoking initiation, nor an association between smoking cessation and ovarian cancer mortality, even 20 years after quitting. Previous studies suggest an increased risk of ovarian cancer incidence associated with current smoking for mucinous epithelial tumors.^{18,19}

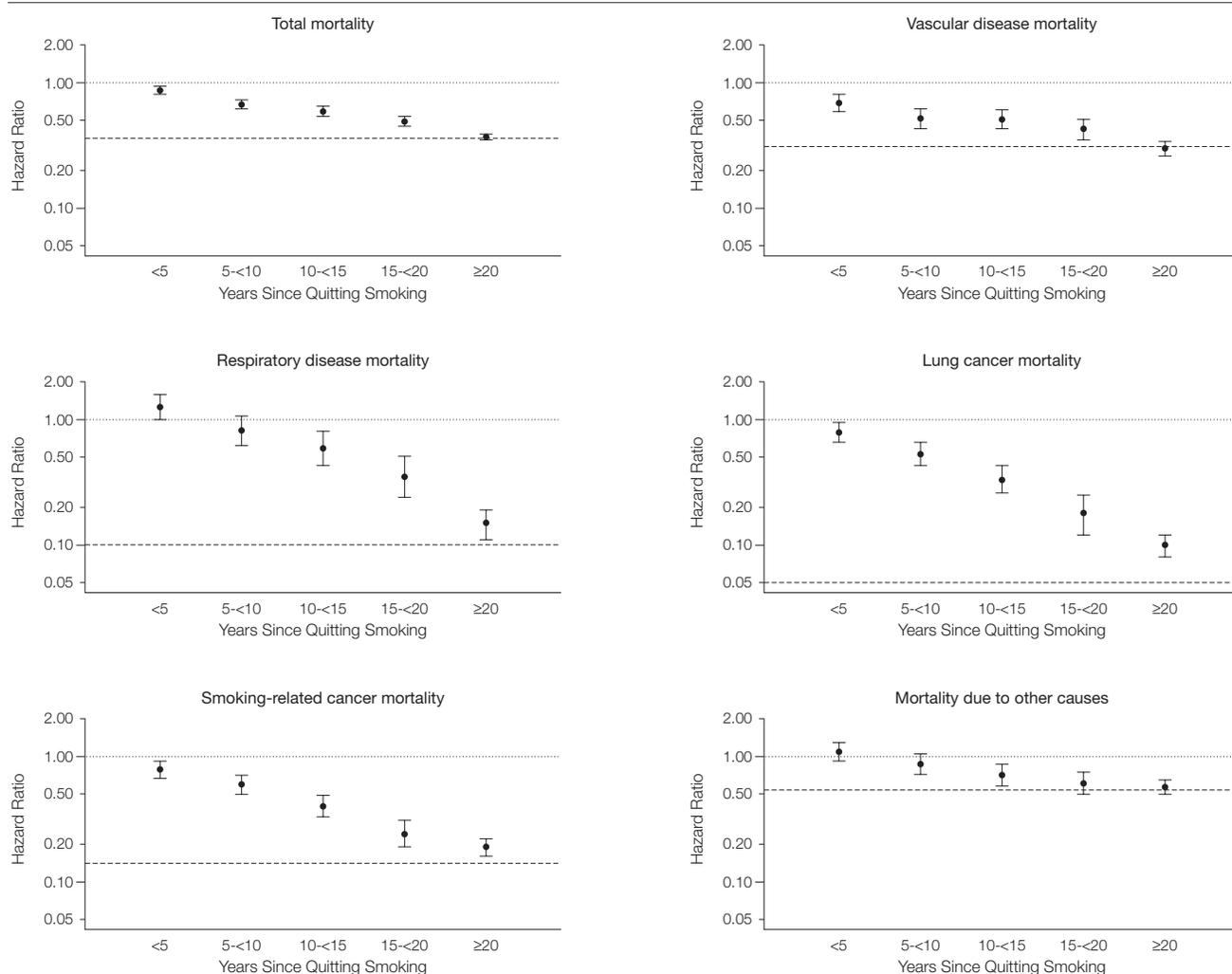
Smoking cessation was beneficial for each cause-specific mortality outcome examined. Unlike the Cancer Prevention Study I, which did not update

smoking status during follow-up and found that the risks associated with lung cancer and COPD mortality remained even after 20 years, we observed a monotonic decrease in risk compared with current smoking with increasing years of smoking cessation, with risks equivalent to those of never smokers after 20 years for COPD and after 30 years for lung cancer.²⁰ By stopping the updating of covariates after diagnosis, we minimized the bias due to symptom-induced smoking cessation or reduc-

ing smoking levels (the “ill quitter” effect). Inability of other studies to update smoking exposure over time or use smoking information just before diagnoses may obscure the harms of continuing smoking and the benefits of cessation because current smokers may quit smoking over time and some past smokers may resume smoking.

In the British Doctors Study, men born in the 1920s were assumed to have more intense early cigarette exposure than earlier birth cohorts,

Figure. Total and Cause-Specific Mortality by Time Since Quitting Smoking Among 104 519 Women in the Nurses’ Health Study From 1980 to 2004



The y-axis is a log scale. The error bars denote 95% confidence intervals. The reference category consists of current smokers. The horizontal dashed line indicates a never-smoker’s risk. Adjusted for age (months), follow-up period, history of hypertension, diabetes, high cholesterol levels, body mass index, change in weight from age 18 years to baseline (1980), alcohol intake, physical activity, previous use of oral contraceptives, postmenopausal estrogen therapy use and menopausal status, parental history of myocardial infarction at age 65 years or younger, cigarettes smoked per day during the period prior to quitting, and age at starting smoking.

and coupled with improvements in treatment, an estimated two-thirds of those persistent smokers were likely to die from smoking.²¹ We did not see differences in early cigarette exposure among women born between 1920 and 1929 compared with women born between 1930 and 1939, translating into similar hazards for total mortality in both groups. However, youth are starting to smoke at younger ages, and one national survey found that 13% of eighth grade students first smoked by age 11 years,²² and 22% of all high school students reported being current smokers.²³ It is likely that deaths attributable to smoking will increase over time unless there is a substantial increase in cessation.

In summary, our findings indicate that 64% of deaths in current smokers and 28% of deaths in past smokers are attributable to smoking. Quitting re-

duces the excess mortality rates for all major causes of death examined. Most of the excess risk of vascular mortality due to smoking may be eliminated rapidly upon cessation and within 20 years for lung diseases, in which the damaging effects of smoking are greatest. Early age at initiation is associated with an increased mortality risk so implementing and maintaining school tobacco prevention programs, in addition to enforcing youth access laws, are key preventive strategies.^{24,25} Effectively communicating risks to smokers and helping them quit successfully should be an integral part of public health programs.

Author Contributions: Drs Kenfield and Colditz had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

Study concept and design: Kenfield, Stampfer, Rosner, Colditz.

Acquisition of data: Kenfield, Stampfer, Colditz.

Analysis and interpretation of data: Kenfield, Stampfer, Rosner, Colditz.

Drafting of the manuscript: Kenfield.

Critical revision of the manuscript for important intellectual content: Kenfield, Stampfer, Rosner, Colditz.

Statistical analysis: Kenfield, Rosner.

Obtained funding: Stampfer, Colditz.

Administrative, technical, or material support: Colditz.

Study supervision: Stampfer, Colditz.

Financial Disclosures: None reported.

Funding/Support: The project was supported by grants R25CA098566 and T32CA09001 from the National Institutes of Health, the Association of Schools of Public Health, and the Legacy Foundation.

Role of the Sponsor: The funding sources had no role in the design or conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

Disclaimer: The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute of the National Institutes of Health, the Association of Schools of Public Health, the Legacy Foundation, the Legacy Foundation staff, or the Legacy Foundation's Board of Directors.

Additional Contributions: We thank the participants and staff of the Nurses' Health Study for their valuable contributions. Special thanks to Weiliang Qiu, PhD (Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts) for his graphical expertise. Dr Qiu was not compensated for his contribution.

REFERENCES

1. US Dept of Health and Human Services. *Women and Smoking: A Report of the Surgeon General*. Rockville, MD: US Dept of Health and Human Services, Public Health Service, Office of the Surgeon General; 2001.
2. Ezzati M, Lopez AD. Estimates of global mortality attributable to smoking in 2000. *Lancet*. 2003;362(9387):847-852.
3. World Health Organization. The tobacco atlas. <http://www.who.int/tobacco/en/atlas11.pdf>. Accessibility verified March 25, 2008.
4. Kawachi I, Colditz GA, Stampfer MJ, et al. Smoking cessation in relation to total mortality rates in women. *Ann Intern Med*. 1993;119(10):992-1000.
5. Colditz GA, Hankinson SE. The Nurses' Health Study: lifestyle and health among women. *Nat Rev Cancer*. 2005;5(5):388-396.
6. US Dept of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General*. Washington, DC: US Dept of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2004.
7. Rich-Edwards JW, Corsano K, Stampfer MJ. Test of the national death index and Equifax nationwide death search. *Am J Epidemiol*. 1994;140(11):1016-1019.
8. Samet JM, Thun MJ, de Gonzalez AB. Models of smoking and lung cancer risk: a means to an end. *Epidemiology*. 2007;18(5):649-651.
9. US Dept of Health and Human Services. *The Health Benefits of Smoking Cessation: A Report of the Surgeon General*. Atlanta, GA: US Dept of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 1990.
10. Sparrow D, Dawber TR. The influence of cigarette smoking on prognosis after a first myocardial infarction: a report from the Framingham study. *J Chronic Dis*. 1978;31(6-7):425-432.
11. Robins J. A graphical approach to the identification and estimation of causal parameters in mortality studies with sustained exposure periods. *J Chronic Dis*. 1987;40(suppl 2):1395-1615.
12. Robins J. The control of confounding by intermediate variables. *Stat Med*. 1989;8(6):679-701.
13. Holmes MD, Murin S, Chen WY, Kroenke CH, Spiegelman D, Colditz GA. Smoking and survival after breast cancer diagnosis. *Int J Cancer*. 2007;120(12):2672-2677.
14. Vineis P, Alavanja M, Buffler P, et al. Tobacco and cancer: recent epidemiological evidence. *J Natl Cancer Inst*. 2004;96(2):99-106.
15. IARC. *Reversal of Risk After Quitting Smoking*. Vol 11. Lyon, France: IARC; 2007.
16. Giovannucci E. An updated review of the epidemiological evidence that cigarette smoking increases risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev*. 2001;10(7):725-731.
17. Chao A, Thun MJ, Jacobs EJ, Henley SJ, Rodriguez C, Calle EE. Cigarette smoking and colorectal cancer mortality in the cancer prevention study II. *J Natl Cancer Inst*. 2000;92(23):1888-1896.
18. Marchbanks PA, Wilson H, Bastos E, Cramer DW, Schildkraut JM, Peterson HB. Cigarette smoking and epithelial ovarian cancer by histologic type. *Obstet Gynecol*. 2000;95(2):255-260.
19. Green A, Purdie D, Bain C, Siskind V, Webb PM. Cigarette smoking and risk of epithelial ovarian cancer (Australia). *Cancer Causes Control*. 2001;12(8):713-719.
20. Burns DM, Shanks TG, Choi W, Thun MJ, Heath CW Jr, Garfinkel L. The American Cancer Society Cancer Prevention Study I: 12-year followup of 1 million men and women. In: Burns DM, Garfinkel L, Samet JM, eds. *Monograph 8: Changes in Cigarette-Related Disease Risks and Their Implications for Prevention and Control*. Bethesda, MD: National Cancer Institute; 1996:113-149.
21. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors [published ahead of print June 22, 2004]. *BMJ*. 2004;328(7455):1519.
22. Johnston LD, O'Malley PM, Bachman JG. *Monitoring the Future National Survey Results on Drug Use, 1975-2002: Volume I, Secondary School Students*. Bethesda, MD: National Institute on Drug Abuse; 2003.
23. Centers for Disease Control and Prevention. 2004 youth tobacco survey. http://www.cdc.gov/tobacco/data_statistics/surveys/NYTS/index.htm. Accessibility verified March 25, 2008.
24. Sussman S, Lichtman K, Ritt A, Pallonen UE. Effects of thirty-four adolescent tobacco use cessation and prevention trials on regular users of tobacco products. *Subst Use Misuse*. 1999;34(11):1469-1503.
25. Stead LF, Lancaster T. A systematic review of interventions for preventing tobacco sales to minors. *Tob Control*. 2000;9(2):169-176.