Age and the Exposure-Response Relationships Between Cigarette Smoking and Premature Death in Cancer Prevention Study II

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INTRODUCTION In the United States and other developed countries, cigarette smoking causes most cases of lung cancer and chronic obstructive pulmonary disease (COPD) (U.S. Department of Health, Education, and Welfare, 1964 and 1979; U.S. Department of Health and Human Services, 1984, 1989, and 1990) and a substantial fraction of deaths from coronary heart disease (CHD) (U.S. Department of Health, Education, and Welfare, 1964, 1971, and 1979; U.S. Department of Health and Human Services, 1983, 1989, and 1990) and stroke (U.S. Department of Health, Education, and Welfare, 1964; U.S. Department of Health and Human Services, 1983, 1989, and 1990). Because of the vast number of deaths caused by tobacco, there is a continuing need to quantify the epidemic, both in developed countries, where cigarette smoking has evolved over several generations (Peto et al., 1992 and 1994), and in other countries, where manufactured cigarettes have only recently been introduced (U.S. Department of Health and Human Services, 1992).

Cancer Prevention Study II (CPS-II), begun by the American Cancer Society (ACS) in 1982 (Garfinkel, 1985; Stellman and Garfinkel, 1986; Garfinkel and Stellman, 1988), is the largest and most recent prospective study of smoking and disease. The large size of the cohort facilitates quantification of the dose-response relation between cigarette smoking and premature mortality and estimation of the smoking-attributable risks for many diseases (Shopland et al., 1991). Relative risk estimates from CPS-II (disregarding dose) already have been used extensively to estimate smoking-attributable mortality in the United States (U.S. Department of Health and Human Services, 1989; Shultz et al., 1991 and 1992), Latin America (U.S. Department of Health and Human Services, 1992), and nearly 50 other developed countries (Peto et al., 1992 and 1994).

This chapter extends previous analyses of CPS-II data by examining the exposure-response relation between current age, years of smoking, cigarettes smoked per day, and premature mortality from major tobacco-related diseases. It considers particularly whether the quantitative relationships differ according to the age of the smoker and the epidemiologic measure used to assess risk. Thun and colleagues (Chapter 4) consider whether these quantitative relationships changed over the time between Cancer Prevention Study I (CPS-I) (1959 through 1965) and CPS-II (1982 through 1988).

BACKGROUND AND ISSUES CONSIDERED

Measures of Increased Risk

The excess risk of mortality of smokers is typically measured as the rate ratio (RR = death rate in smokers divided by that in lifelong nonsmokers) (Rothman, 1986; Cornfield and Haenszel, 1960). An alternative measure is the rate difference (RD = death rate in smokers minus that in never-smokers) (Rothman, 1986). These measures provide different insights into the risk associated with smoking. The RR generally is used to assess etiologic or causal associations. It expresses the death rate among smokers as a multiple of that in never-smokers, indirectly reflecting the proportion of deaths attributable to smoking among the exposed. The RD represents the absolute increase in death rates among exposed persons. It reflects more directly the burden of premature mortality on individuals and society (Rothman, 1986).

The Effect of Age on the RR and RD

Age-related factors profoundly influence many chronic diseases. Because background death rates are included in the calculations of both the RR and RD, age-related changes in background risk potentially influence both measures. For CHD and stroke in particular, hypertension and other age-related factors cause mortality to increase dramatically with age in nonsmokers as well as in smokers (U.S. Department of Health and Human Services, 1983). In countries where background CHD mortality is high, the age-related increase in background risk causes the RR to decrease and the RD to increase with aging (Hennekens et al., 1984). In the British Doctors Study, death rates from CHD were 5.7 times higher among cigarette smokers than among nonsmokers at ages 35 to 44 but were approximately equal to those of nonsmokers at ages 75 to 84 (Doll and Hill, 1966; Rothman, 1986). Similar patterns were seen in CPS-I (Hammond, 1966) and the U.S. Veterans' Study (Kahn, 1966). Although the age-related changes in RR have not been emphasized, calculations of deaths from smoking have considered at least two age groups (35 to 64, ≥65) in estimating deaths from CHD and stroke in several recent reports on smoking and disease (Peto et al. 1992 and 1994; U.S. Department of Health and Human Services, 1992).

Age and Susceptibility to Cancer

There are at least two hypotheses on the relationship of age to cancer risk; these arguments have been extended to lung cancer and smoking. Peto and colleagues (1975 and 1985) contend that increasing age alone does not increase biologic susceptibility to cancer but merely allows time for exposures to accumulate, genetic damage to occur, and tumors to become manifest. Others theorize that aging impairs immunity, reduces DNA (deoxyribonucleic acid) repair, and causes loss of cell regulation, which may amplify injury by carcinogens (Anisimov, 1989; Miller, 1991; Holiday, 1984). Understanding the relative effects of age and years of smoking is particularly important in an era when many cigarette smokers begin smoking in adolescence and continue through life. The concept that age might accelerate the carcinogenic process has potential implications for both cancer prevention and research emphasis.

Age, Years of Smoking, and Cigarettes Smoked Per Day

Most studies have not been large enough to sharply separate the effects of age, years of smoking, and daily cigarette consumption. Widely cited and informative analyses were published by Doll and Peto (Doll and Peto, 1978; Peto, 1986) based on a 20-year followup of the British Doctors Study (Doll and Peto, 1976). Among men who currently were smoking ≤40 cigarettes per day and who began smoking between ages 16 and 25, lung cancer incidence was proportional to the fourth or fifth power of duration, as estimated by [age (in years)—22.5], but only to the second power of the number of cigarettes smoked per day (Doll and Peto, 1978; Peto, 1986). Age-22.5 served as a proxy for the number of years of smoking. The results have been widely interpreted as showing that the duration of smoking has a greater effect on lung cancer risk than does the daily number of cigarettes smoked (Moolgavkar et al., 1989; Higgenson, 1988). However, the statistical modeling was based on only 124 cases of lung cancer (Doll and Peto, 1978), and the use of age-22.5 to reflect duration left open the possibility that older smokers might be more susceptible to a given duration of smoking and amount of daily cigarette consumption because effect modification by age could not be assessed in these analyses (Moolgavkar et al., 1989; U.S. Department of Health and Human Services, 1990; Wu-Williams and Samet, 1994; Burns, 1994).

CPS-II provides an unusual opportunity to examine age as a potential modifier of the effect of smoking because the study provides direct information on both age and years of smoking, includes 3,229 lung cancer deaths, and is sufficiently large to support stratified analyses, which require fewer assumptions than statistical modeling.

SUBJECTS AND METHODS

Subjects in the analyses were drawn from CPS-II (Garfinkel, 1985; Garfinkel and Stellman, 1988), a nationwide prospective mortality study of 1,185,106 men and women, begun by the ACS in 1982.

Selection Criteria

CPS-II subjects were recruited by ACS volunteers in all 50 States, the District of Columbia, Puerto Rico, and Guam. Volunteers contacted their friends, neighbors, and acquaintances and sought to enroll all household members age 30 or older if at least one family member was 45 years or older (Garfinkel, 1985). A similar approach was used effectively in the Hammond-Horn or 10-State study (Hammond and Horn, 1958a and 1958b) and the CPS-I (Hammond, 1964 and 1966; Hammond and Garfinkel, 1961; U.S. Department of Health and Human Services, 1990).

Followup

The authors' analyses are based on 6-year followup, from the month of enrollment in 1982 through August 31, 1988. In this interval, the participants' vital status was determined every 2 years through personal contact by the volunteers. The analyses were restricted to deaths identified by the volunteers during the first 6 years. In the entire cohort, 79,802 participants (6.7 percent) had died, 1,083,600 (91.4 percent) were alive, and 21,704 (1.8 percent) were lost to followup during this interval. Persons lost to followup were considered alive until the end of followup. Death certificates were obtained for 94.1 percent of the persons known to have died. The underlying cause of death was coded according to an

abbreviated version of the *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death (ICD-9)* (World Health Organization, 1977).

Information on Tobacco Smoking At enrollment, participants completed a four-page questionnaire on demographic and lifestyle factors, including tobacco use (questions on smoking appear as Appendix 1). The distribution of smoking responses among all CPS-II participants is shown in Table 1. "Never-smokers," subsequently called nonsmokers, were persons who answered "no" to question 2 and did not respond to questions 3 through 7. "Current cigarettes only" included persons who answered "yes" to question 2, who had never smoked pipes or cigars, and who left blank the questions on former smoking. Current smokers were considered to have complete data if they specified the "age began smoking" and "average number smoked per day." The duration of smoking was defined as "total years smoked" reported by the respondent or, if missing, the difference between age of initiation and age at enrollment. In the dose-response analyses, duration was considered fixed at the time of enrollment, except as otherwise specified. However, person-years of observation (PYO's) and deaths accrued at the age of the individual during the year of followup. That is, smokers were considered to be continuing smokers for purposes of age classification (age was advanced), but the years of smoking were fixed at entry into the study.

Analytic Cohort All analyses were restricted to 482,681 lifelong nonsmokers and 228,682 current cigarette (only) smokers with complete data on years of smoking and daily cigarette consumption. We excluded former cigarette smokers, persons ever smoking pipes or cigars, and those whose smoking status was unclassifiable (Table 1). Dose-response analyses were further restricted to persons ages 50 to 79 years who were either lifelong nonsmokers or current cigarette smokers of ≥20 years duration on enrollment.

Rate Comparisons in Never-Smokers and Current Smokers We compared death rates from lung cancer (*ICD-9*, 162), CHD (*ICD-9*, 410-414), stroke (*ICD-9*, 430-438), COPD (*ICD-9*, 490-492, 496) (World Health Organization, 1977), and all combined causes of death among current cigarette smokers and lifelong nonsmokers. The numerators used in calculating the rates were age-, gender-, and cause-specific deaths as coded by underlying (Tables 2 through 12) or contributing (Appendixes 2 and 3) causes of death as stated on death certificates. The denominators were person-years at risk within the corresponding age and gender (Appendix 4). Figures 1 through 10, using age-specific death rates, RR's, and RD's, illustrate how age modifies the apparent effect of smoking on premature mortality. Age-adjusted death rates (Tables 2 through 12) were directly standardized to the 1980 U.S. population (Appendix 5) (U.S. Department of Health and Human Services, 1985). Ninety-five percent confidence intervals for the age-adjusted RR's and RD's were calculated using approximate variance formulas (Rothman, 1986). For each fatal endpoint, we calculated the percentage of deaths attributable to smoking among all current cigarette smokers (Table 4) ([death rate in smokers minus rate in nonsmokers]/death rate in smokers) × 100, or alternatively

Table 1
Smoking habits of Cancer Prevention Study II participants

	Men		Women		
Smoking Habits	N	%	N	%	Total
Never-Smokers[a]	127,163	(25.0)	355,518	(52.6)	482,681
Current Cigarettes Only					
Data complete	101,888	(20.0)	126,794	(18.7)	228,682
Data incomplete[b]	3,196	(0.6)	8,298	(1.2)	11,494
Former Cigarettes Only					
Data complete	140,988	(27.7)	122,059	(18.0)	263,047
Data incomplete[b]	9,558	(1.9)	16,896	(2.5)	26,454
Ever Pipe or Cigar	101,600	(20.0)	NA[c]	NA[c]	101,600
Unclassifiable	24,186	(4.8)	46,962	(6.9)	71,148
Total	508,579		676,527		1,185,106
Total in Analyses[d]	229,051		482,312		711,363

[a] "Never-smokers" defined as never having smoked at least one cigarette, cigar, or pipe daily for 1 year's time.
[b] Data missing on years of smoking or daily cigarette consumption.
[c] Women not asked about pipe or cigar smoking.
[d] Excludes persons with incomplete or unclassifiable data, former smokers, and those who ever smoked pipes or cigars.

Key: NA = not available.

(RR–1/RR) × 100 (Rothman, 1986). We estimated this smoking-attributable fraction (SAF) within 5-year age intervals and over all ages.

Exposure-Response Analyses We calculated death rates from lung cancer, CHD, and all combined causes of death by attained age (50 to 59, 60 to 69, 70 to 79), years of smoking at baseline (20 to 29, 30 to 39, 40 to 49, ≥50), cigarettes smoked per day (1 to 19, 20, 21 to 39, 40, 41+), and sex (Appendixes 6 through 17). Stratification was possible only for the most common diseases in persons ages 50 to 79 and those reporting at least 20 years of smoking. Within each stratum of age, smoking, and sex we measured the RR and RD compared with lifelong nonsmokers of comparable age and sex.

Figure 11 shows the RD values for lung cancer in relation to cigarette exposure using three rather than five categories of cigarettes per day (Appendixes 18 through 21) to increase the stability of the rate estimates. All the RD values based on three or more deaths in both smokers and nonsmokers were positive. However, those based on fewer than three deaths (not shown) were sometimes negative. We did not use these values. We repeated the analyses allowing the years of smoking to progress during followup as well as age (Appendixes 22 through 25). Based on a comparison of Appendixes 18 through 21 and 22 through 25, we assessed whether

continued smoking during followup was distorting the apparent effect of age on the exposure-response relationships.

Many other exposure-response analyses not discussed here are included in the appendixes for archival purposes. These stratify on either age and cigarettes per day (Appendixes 26 through 37) or age and years of smoking (Appendixes 38 through 59) but not on all three variables simultaneously.

Stratified vs. Standardized Exposure-Response Analyses

The description of exposure-response relationships over all ages was constrained by several factors. First, even in a large study like CPS-II, cause-specific deaths and person-years at risk are sparse when stratified simultaneously by several variables. Although broader categories of age and years of smoking might improve the statistical power of subgroup analyses, there would be concern for residual confounding. Second, because most deaths caused by smoking occurred at least 30 years after initiation and because age and years of smoking were strongly collinear, the PYO's largely lie along the diagonal from middle age/medium duration to old age/long duration. Death rates in cells off this diagonal were estimated poorly because there were essentially no PYO's. Neither direct nor indirect standardization could be used to summarize the effect of years of smoking across all age strata. Direct standardization would necessarily assign finite weights to empty cells, treating these rates as zeros rather than as unmeasurable. Indirect standardization would weight smokers with short duration more heavily toward younger ages and long-term smokers toward older ages.

RESULTS

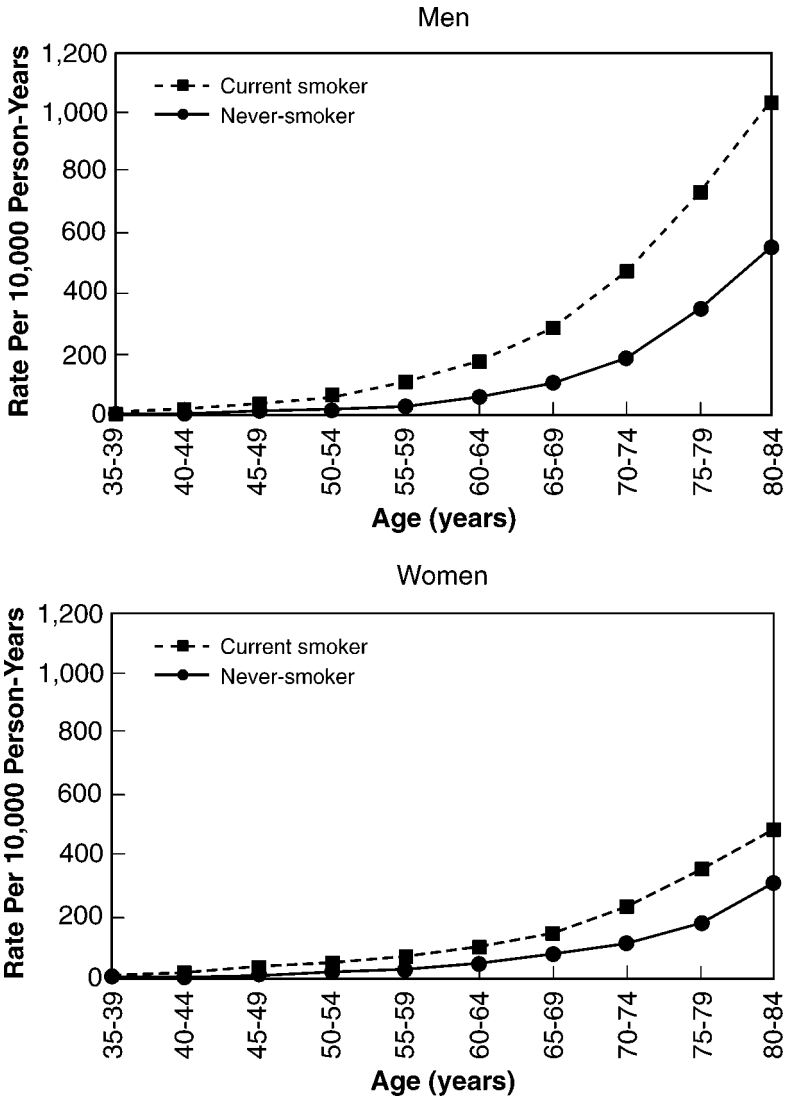
Never-Smokers vs. Current Smokers

Death rates from all combined causes were substantially higher in men and women who smoked cigarettes than in lifelong nonsmokers (Figure 1 and Tables 2 and 3). Because the death rates increased more steeply with age in smokers than in nonsmokers (Figure 1), the absolute difference in death rates (RD) increased with the age of the smoker (Figure 2). The RD associated with any current cigarette smoking peaked among smokers at 4,981.3 deaths per 100,000 person-years in men (Table 2) and 1,805 in women (Table 3) at the oldest ages. (Note: Death rates in Figure 1 are presented per 10,000 person-years, whereas those in Tables 2 and 3 are per 100,000.)

All Causes of Death

In contrast, when the death rate in smokers was expressed relative to that in nonsmokers, the effect of smoking as reflected by the RR decreased rather than increased beyond age 65 (Figure 2). Among men, all-cause death rates between ages 35 and 59 were about three times higher in smokers than nonsmokers, whereas rates were 1.9 times higher at age 80 and older (Table 2). Among women, the all-cause RR peaked at 2.3 times higher for smokers vs. nonsmokers at ages 60 to 69 and decreased to 1.6 times higher in the oldest age group (Table 3). The decline in the all-cause RR with age indicates that, even though the death rate of smokers increases faster with age than that of nonsmokers, it does not keep pace on a multiplicative scale with the rising background risk in nonsmokers beyond age 59 in men and age 69 in women.

Figure 1
All-cause death rates in current cigarette smokers and lifelong nonsmokers, by age and sex



The age-related decline in RR also implies that the percentage of deaths from all causes attributable to smoking decreases among older cigarette smokers (Table 4). This proportion varies with the RR; in CPS-II it peaked at 69 percent among male smokers ages 40 to 44 (Table 4) and at 57 percent among female smokers ages 65 to 69. Among smokers of all ages, 52 percent of deaths in men and 43 percent in women were attributable to smoking.

Table 2
All-cause mortality among lifelong nonsmokers and current cigarette smokers: Men, Cancer Prevention Study II

	Age Specific					
	Nonsmokers		Current Cigarette Smokers			
Age	Deaths	Rate[a]	Deaths	Rate[a]	RR	RD[a]
35-39	16	72.9	37	219.3	3.0	146.4
40-44	21	93.7	65	303.6	3.2	209.9
45-49	102	151.8	268	427.1	2.8	275.3
50-54	283	221.4	800	678.5	3.1	457.1
55-59	487	367.7	1,367	1,083.8	3.0	716.0
60-64	815	672.6	1,925	1,824.2	2.7	1,151.7
65-69	1,120	1,096.7	1,984	2,884.9	2.6	1,788.2
70-74	1,321	1,846.6	1,760	4,664.5	2.5	2,817.9
75-79	1,389	3,441.2	1,113	7,321.7	2.1	3,880.5
80+	981	5,466.5	434	10,447.8	1.9	4,981.3
Total	6,535		9,753			

	Age Standardized to 1980 U.S. Population	
	Nonsmokers	Current Cigarette Smokers
Death Rate[a]	751.7	1,560.0
Rate Ratio	1.0	2.1
(95% CI)	–	(2.0-2.2)
Rate Difference[a]	–	808.1
(95% CI)	–	(750.6-865.5)

[a] Death rate and rate difference per 100,000 person-years.

Key: RR = rate ratio; RD = rate difference; CI = confidence interval.

Lung Cancer Death rates from lung cancer (per 100,000 person-years) diverged markedly with age between smokers and nonsmokers (Figure 3 and Tables 5 and 6). Background death rates were much lower for lung cancer than for other diseases in nonsmokers but increased rapidly between ages 45 and 74 years in smokers (Figure 3). Figure 4 illustrates that the absolute difference (RD) between the rates of smokers and nonsmokers increased dramatically with age, especially in men. However, the ratio of death rates (RR) was biphasic, first increasing (in men) and later decreasing (in both sexes). The RR in men increased from 7 (at ages 45 to 49) to 39 (at ages 55 to 59) and then decreased to 13.8 (at age 80 and older) (Table 5). In women, there were insufficient observations to evaluate death rates in those younger than age 45, but the RR decreased from 22.1 at ages 45 to 49 years to 7.3 at age 80 and older (Table 6).

Much less variability with age occurred in the percentage of fatal lung cancers attributable to smoking (SAF, Table 4) than in the RR (Table 5 and Figure 4). The SAF among smokers averaged 95 percent in men and

Table 3
All-cause mortality among lifelong nonsmokers and current cigarette smokers: Women, Cancer Prevention Study II

	Age Specific					
	Nonsmokers		Current Cigarette Smokers			
Age	Deaths	Rate[a]	Deaths	Rate[a]	RR	RD[a]
35-39	40	80.6	22	88.8	1.1	8.2
40-44	93	109.3	50	110.9	1.0	1.6
45-49	255	122.4	256	252.6	2.1	130.2
50-54	564	182.1	501	348.5	1.9	166.4
55-59	927	268.2	874	598.8	2.2	330.6
60-64	1,401	411.4	1,140	936.3	2.3	525.0
65-69	1,871	666.5	1,243	1,533.7	2.3	867.2
70-74	2,216	1,073.9	1,020	2,227.0	2.1	1,153.1
75-79	2,487	1,838.7	658	3,417.9	1.9	1,579.1
80+	2,245	3,154.2	285	4,959.2	1.6	1,805.0
Total	12,099		6,049			

	Age Standardized to 1980 U.S. Population	
	Nonsmokers	Current Cigarette Smokers
Death Rate[a]	485.5	842.8
Rate Ratio	1.0	1.8
(95% CI)	–	(1.7-1.8)
Rate Difference[a]	–	357.3
(95% CI)	–	(320.4-394.2)

[a] Death rate and rate difference per 100,000 person-years.

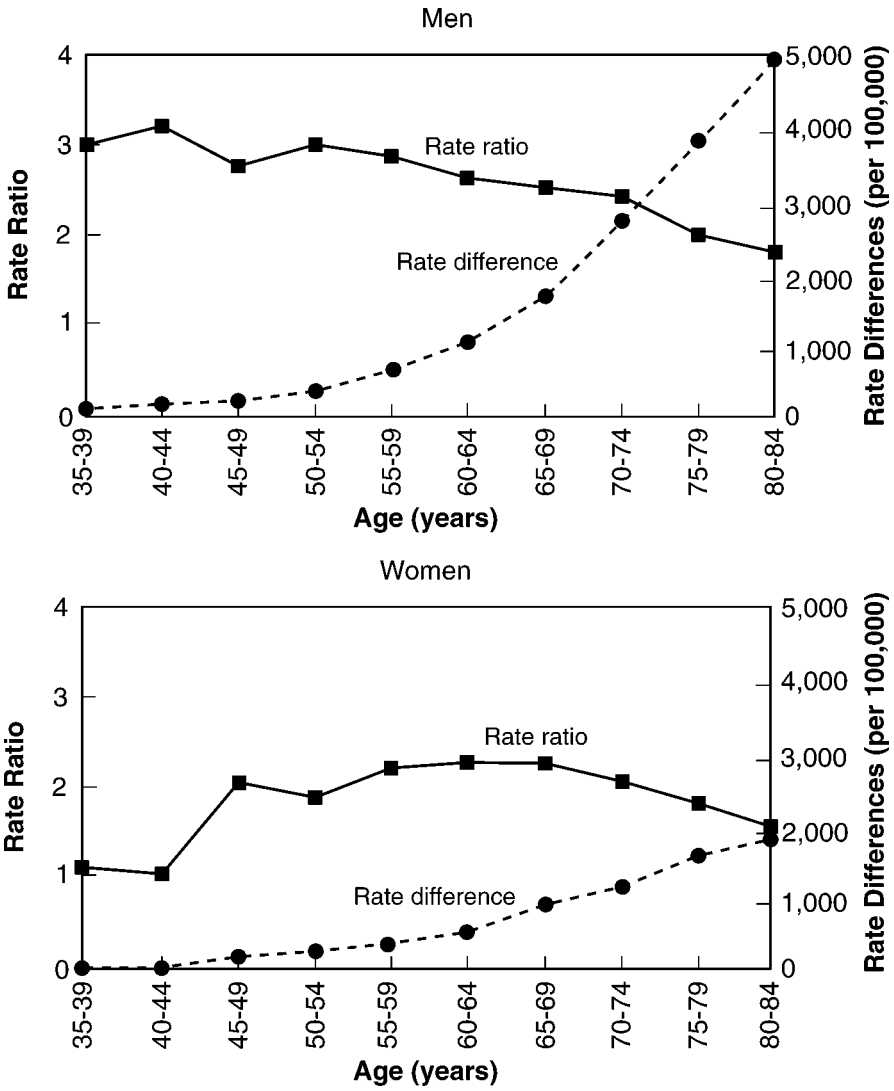
Key: RR = rate ratio; RD = rate difference; CI = confidence interval.

92 percent in women in all age 35 and older combined, always exceeding 85 percent (Table 4). The relative stability of this measure reflects the nonlinear relation between it and the RR (SAF = (RR–1)/RR × 100); 50 percent of its impact occurs as the RR decreases from 2.0 to 1.0. RR values above 10 (Table 5 and Figure 4) correspond to SAF values above 90 percent (Table 4).

Coronary Heart Disease

Age-specific death rates from coronary heart disease followed a pattern similar to that for all-cause mortality; smokers had higher death rates at all ages, yet the background risk among nonsmokers rose substantially with age (Figure 5). Consequently, the difference in death rates (RD) rose progressively with age (for women it declined slightly only for those older than age 79), whereas the ratio (RR) peaked at 6.3 in men (ages 40 to 44) and at 7.2 in women (ages 45 to 49) and declined progressively with further aging (Figure 6 and Tables 7 and 8). The percentage of CHD deaths attributable to smoking among cigarette smokers declined more dramatically with age than did the percentage of lung cancer deaths (increasing slightly

Figure 2
All-cause rate ratios and rate differences in current cigarette smokers and lifelong nonsmokers, by age and sex



only in men age 80 and older) (Table 4). The SAF decreased in men from 84 percent at ages 40 to 44 years to 26 percent at ages 75 to 79 years and in women from 86 percent at ages 45 to 49 years to 23 percent at age 80 and older. As the RR approached 1.0 at older ages (Tables 7 and 8), the attributable percentage (Table 4) diminished rapidly, as anticipated.

Stroke

Age-specific patterns of stroke mortality (Figures 7 and 8, Tables 9 and 10) were similar to those seen with CHD. The RD's increased progressively with age, whereas the RR's in men followed a biphasic pattern and in women

Table 4
Percentage of deaths attributable to smoking (SAF)[a] among current cigarette smokers in Cancer Prevention Study II

	Age										
	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80+	All Ages Combined
Men											
Lung cancer	–	–	86	95	97	97	96	96	95	93	95
CHD	69	84	82	74	63	58	47	41	26	31	41
Stroke	–	–	73	80	75	63	62	49	47	31	36
COPD	–	–	–	88	90	92	95	90	93	91	91
All causes	67	69	64	67	66	63	62	60	53	48	52
Women											
Lung cancer	–	–	95	91	94	93	94	90	92	86	92
CHD	–	–	86	82	68	62	59	47	38	23	37
Stroke	–	–	87	79	83	61	62	63	50	–	28
COPD	–	–	–	92	89	91	93	92	91	92	93
All causes	9	2	51	48	55	56	57	52	46	36	43

[a] Smoking-attributable fraction (SAF) = $\frac{(RR-1)}{RR} \times 100$. SAF for all ages is based on RR values directly standardized to 1980 U.S. age distribution.

Key: CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; RR = rate ratio.

fluctuated somewhat before decreasing consistently after age 74. The percentage of fatal strokes attributable to cigarette smoking also declined dramatically with age among smokers (Table 4). In men this fraction fell from 80 percent at ages 50 to 54 years to 31 percent at ages ≥80 years; in women it decreased erratically from 87 percent at ages 45 to 49 years to virtually 0 percent at ages ≥80 years.

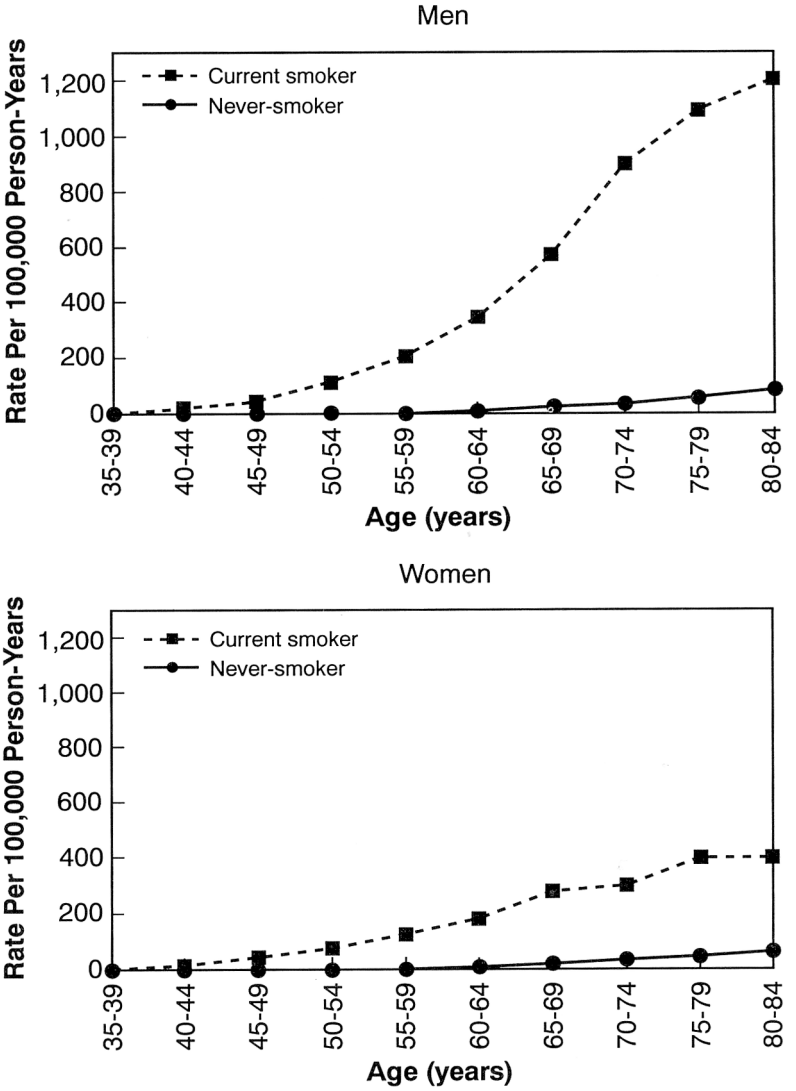
Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease resembled lung cancer in the wide divergence in death rates between smokers and nonsmokers (Figure 9) and the high proportion of deaths attributable to cigarettes among smokers (Tables 4, 11, and 12). Although the RD's consistently increased with age (Figure 10), the RR's fluctuated somewhat erratically between 8 and 19 in men (Table 11) and between 9.5 and 15 in women (Table 12). The SAF remained at or above 88 percent at all ages in both sexes.

Summary of Rates in Current Smokers vs. Lifelong Nonsmokers

The magnitude of the adverse effects of cigarette smoking on mortality among all smokers differed quantitatively depending on the disease, the age and sex of the smoker, and the epidemiologic measure used to assess risk. The absolute risk of a smoker dying prematurely in CPS-II increased with the age of the smoker, whereas the relative risk first increased and then decreased with age. The percentage of deaths attributable to smoking (SAF) varied more with age for cardiovascular diseases than for lung cancer or COPD because the

Figure 3
Lung cancer death rates in current cigarette smokers and lifelong nonsmokers, by age and sex



mathematical relation between the RR and attributable risk was nonlinear and the attributable percentage decreased rapidly as the RR approached 1.0.

Dose-Response Among Current Cigarette Smokers

Whereas the previous analyses considered mortality risks among all cigarette smokers together in relation to age, the next section examines the separate and joint effects of age, years of smoking, and current daily cigarette consumption on death rates.

Table 5
Mortality from lung cancer as underlying cause of death among lifelong nonsmokers and current cigarette smokers: Men, Cancer Prevention Study II

	Age Specific					
	Nonsmokers		Current Cigarette Smokers			
Age	Deaths	Rate[a]	Deaths	Rate[a]	RR	RD[a]
35-39	1	4.6	1	5.9	–	1.4
40-44	0	–	4	18.7	–	18.7
45-49	4	6.0	26	41.4	7.0	35.5
50-54	7	5.5	136	115.3	21.1	109.9
55-59	7	5.3	260	206.1	39.0	200.8
60-64	14	11.6	381	361.1	31.3	349.5
65-69	22	21.5	400	581.6	27.0	560.1
70-74	25	34.9	343	909.0	26.0	874.1
75-79	21	52.0	170	1,118.3	21.5	1,066.3
80+	16	89.2	51	1,227.7	13.8	1,138.6
Total	117		1,772			

	Age Standardized to 1980 U.S. Population	
	Nonsmokers	Current Cigarette Smokers
Death Rate[a]	11.3	229.4
Rate Ratio	1.0	20.3
(95% CI)	–	(16.4-25.1)
Rate Difference[a]	–	218.1
(95% CI)	–	(202.0-234.2)

[a]Death rate and rate difference per 100,000 person-years.

Key: RR = rate ratio; RD = rate difference; CI = confidence interval.

Lung Cancer Dose-Response

Figure 11 illustrates that the excess death rates (RD) from lung cancer increased with age, years of smoking, and cigarettes smoked per day. In this stratified presentation, death rates within each subgroup of age, cigarette smoking, and sex (e.g., men ages 60 to 69 who at enrollment had smoked 1 to 19 cigarettes per day, for 20 to 29 years) were compared with rates in age-comparable lifelong nonsmokers (Appendixes 18 to 21 and Tables 5 and 6). In men, the RD was higher in older smokers than in younger smokers for a comparable amount of reported smoking. For example, men ages 60 to 69 who had smoked for 20 to 29 years and reported smoking 1 to 19 cigarettes per day currently had excess death rates from lung cancer similar to those of younger men, ages 50 to 59, who had smoked for 10 to 29 years longer (Figure 11 and Appendix 20). There is potential for substantial residual confounding between age and years of smoking within these 10-year categories, and the confounding may be particularly strong \in the 50-plus duration category. Such residual confounding limits interpretation of the differences in age-specific rates for duration-specific categories in Figure 11 and Appendix 20. However, within these broad

Table 6
Mortality from lung cancer as underlying cause of death among lifelong nonsmokers and current cigarette smokers: Women, Cancer Prevention Study II

	Age Specific					
	Nonsmokers		Current Cigarette Smokers			
Age	Deaths	Rate[a]	Deaths	Rate[a]	RR	RD[a]
35-39	1	2.0	1	4.0	–	2.0
40-44	0	–	4	8.9	–	8.9
45-49	4	1.9	43	42.4	22.1	40.5
50-54	18	5.8	93	64.7	11.3	58.9
55-59	25	7.2	175	119.9	16.6	112.7
60-64	42	12.3	215	176.6	14.3	164.3
65-69	47	16.7	232	286.3	17.1	269.5
70-74	63	30.5	142	310.0	10.2	279.5
75-79	44	32.5	77	400.0	12.3	367.5
80+	41	57.6	24	417.6	7.3	360.0
Total	285		1,006			

	Age Standardized to 1980 U.S. Population	
	Nonsmokers	Current Cigarette Smokers
Death Rate[a]	8.6	101.3
Rate Ratio	1.0	11.9
(95% CI)	–	(10.1-13.7)
Rate Difference[a]	–	92.7
(95% CI)	–	(83.7-101.7)

[a] Death rate and rate difference per 100,000 person-years.

Key: RR = rate ratio; RD = rate difference; CI = confidence interval.

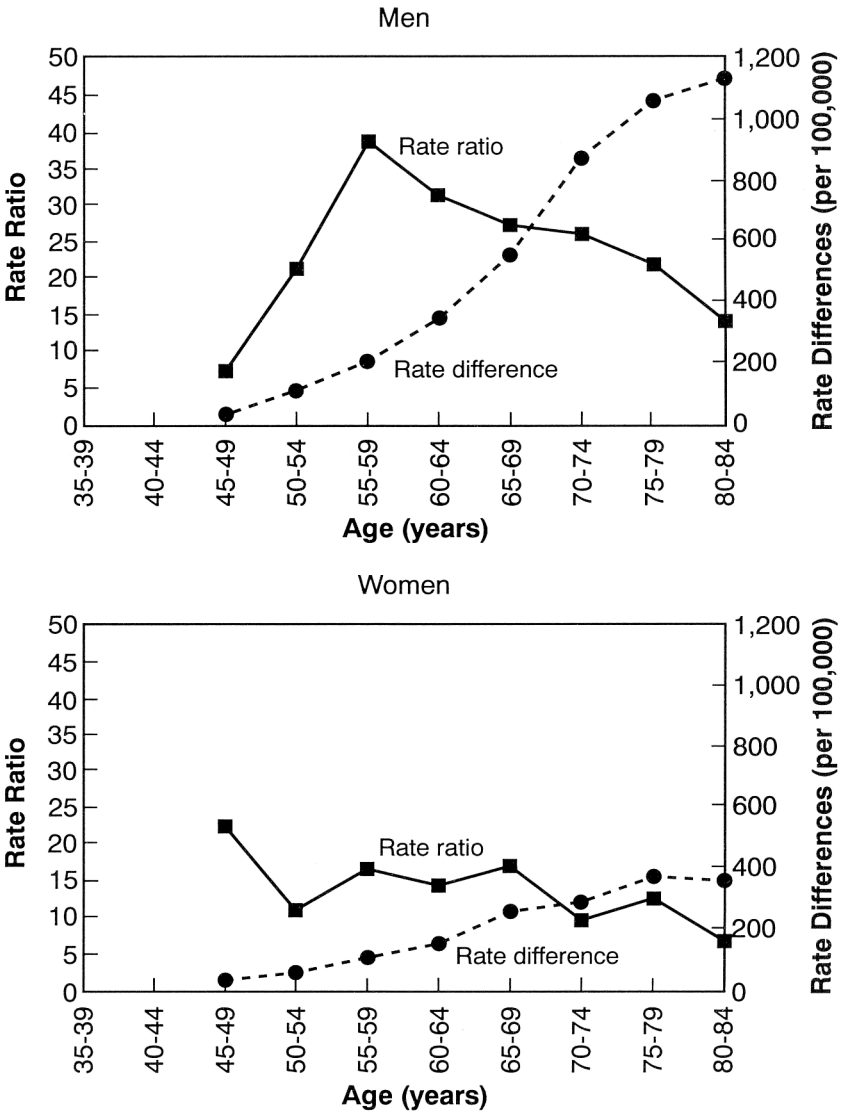
intervals of age, years of smoking, and daily cigarette consumption, older males, but not females, have consistently higher excess lung cancer death rates (RD) than younger individuals in the same duration category.

Coronary Heart Disease and All-Cause Mortality

Appendixes 10 to 17 present exposure-response data on CHD and all-cause mortality stratified by age, years of smoking, and current daily cigarette consumption. Interpretation of these data as complicated by substantial potential for selection bias. Persons who experience nonfatal symptoms of CHD or who reduce their smoking because of other known risk factors may thereby distort the underlying dose-response relationships. This potential for survivor bias among older persons who continue to smoke heavily is greater for CHD than for lung cancer. The all-cause mortality pattern represents a hybrid of major smoking-related diseases and is similarly vulnerable to selection bias among older smokers.

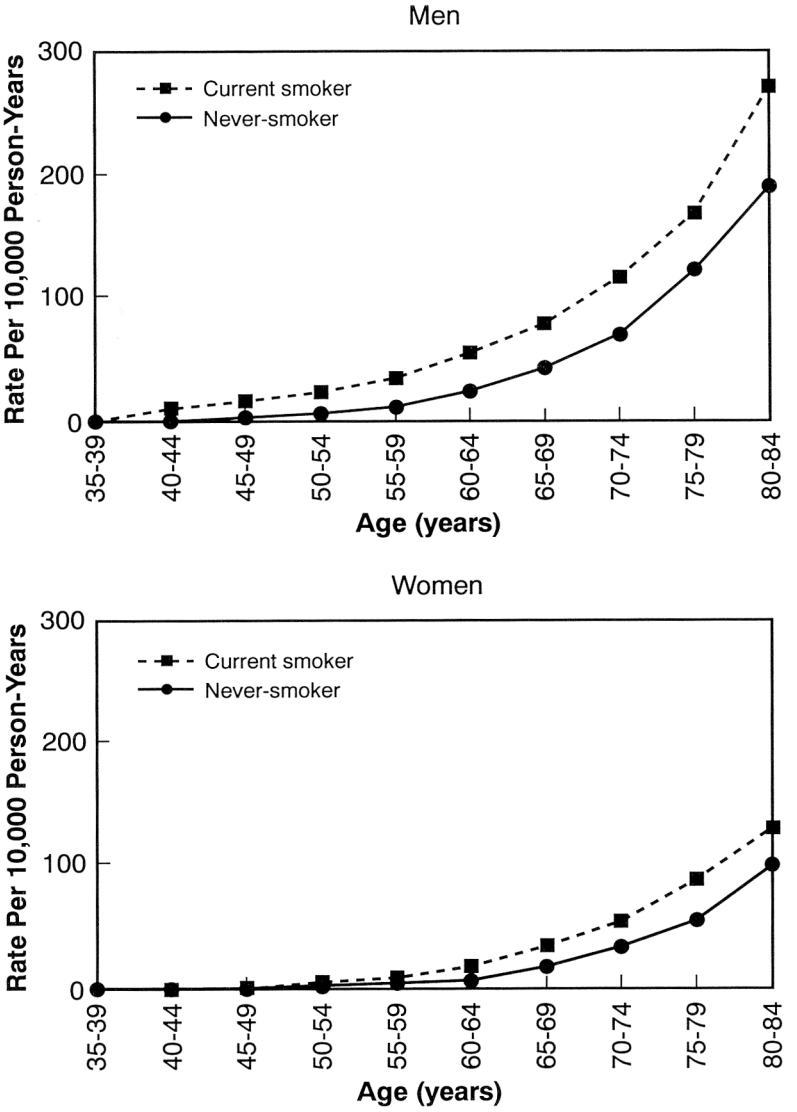
DISCUSSION Our principal findings were that active cigarette smoking consistently and strongly increased the risk of death from lung cancer, CHD, stroke,

Figure 4
Lung cancer rate ratios and rate differences in current cigarette smokers and lifelong nonsmokers, by age and sex



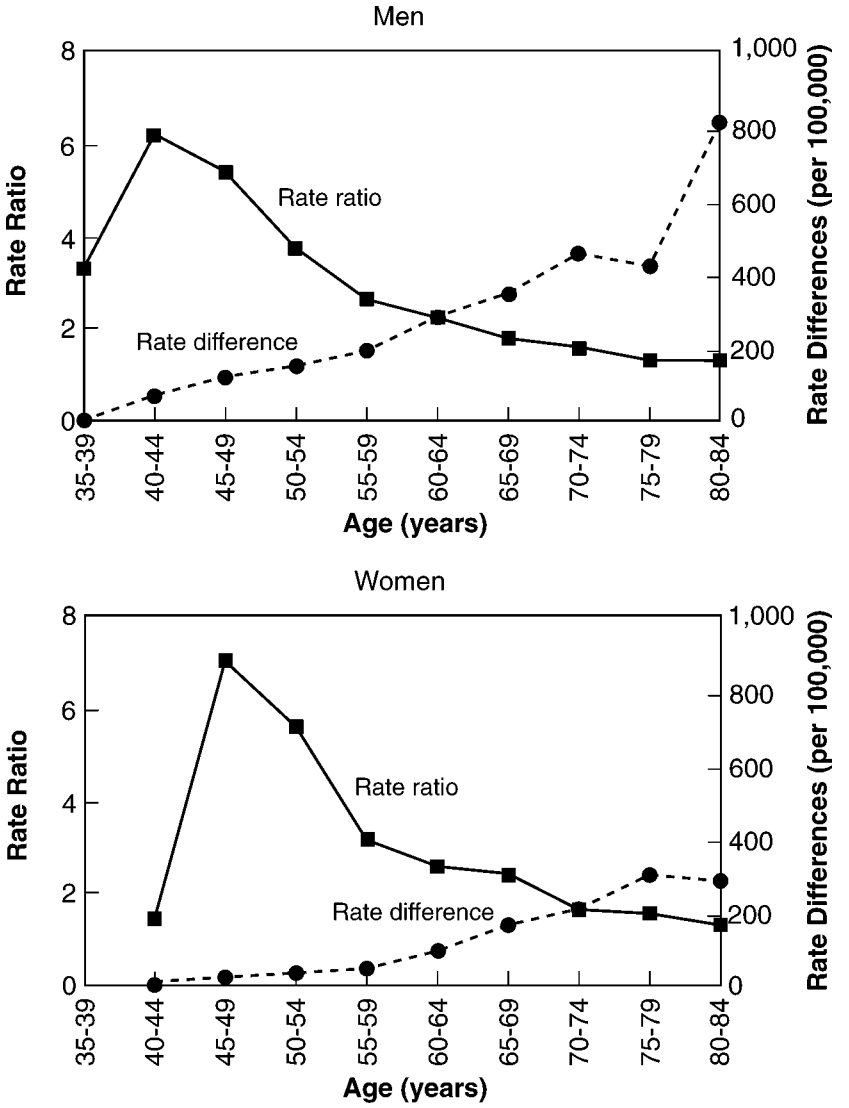
COPD, and death from all causes. However, the magnitude of these adverse effects differed depending on the cause-of-death category, the smoker's age, the number of years of smoking, and the number of cigarettes smoked per day. Relative and absolute measures of risk had different patterns of variation with age for some outcomes. Our results have different implications for the various audiences, including individuals who smoke, epidemiologists who measure the impact of the evolving tobacco epidemic, and researchers interested in carcinogenesis.

Figure 5
Coronary heart disease death rates in current cigarette smokers and lifelong nonsmokers, by age and sex



Significance to Smokers The enormous contribution of cigarette smoking to premature mortality is evident: An estimated 52 percent of deaths in men and 43 percent of deaths in women who continued to smoke were attributable to smoking. This percentage has been rising in U.S. women (Chapter 4) because women began to smoke during adolescence later in this century than did U.S. men. CPS-II demonstrates that the absolute risk of a smoker being killed by cigarette smoking increases rather than decreases with age. Because some

Figure 6
Coronary heart disease rate ratios and rate differences in current cigarette smokers and lifelong nonsmokers, by age and sex



of this risk is reversible (Shopland et al., 1991), an important message for smokers is that "the damage is not yet done." The 1990 U.S. Surgeon General's Report shows that smokers who quit by age 50 experience only modest increased mortality compared with lifelong nonsmokers and that there are substantial benefits from quitting at any age (Shopland et al., 1991). Middle-aged smokers should be considered a high-priority group for smoking cessation programs and for research to improve the success rate of attempted quitting.

Table 7

Mortality from coronary heart disease as underlying cause of death among lifelong nonsmokers and current cigarette smokers: Men, Cancer Prevention Study II

	Age Specific					
	Nonsmokers		Current Cigarette Smokers			
Age	Deaths	Rate[a]	Deaths	Rate[a]	RR	RD[a]
35-39	2	9.1	5	29.6	3.3	20.5
40-44	3	13.4	18	84.1	6.3	70.7
45-49	18	26.8	92	146.6	5.5	119.8
50-54	72	56.3	251	212.9	3.8	156.6
55-59	157	118.6	407	322.7	2.7	204.1
60-64	277	228.6	576	545.9	2.4	317.3
65-69	414	405.4	531	772.1	1.9	366.7
70-74	490	685.0	437	1,158.2	1.7	473.2
75-79	497	1,231.3	254	1,670.9	1.4	439.6
80+	340	1,894.6	113	2,720.3	1.4	825.7
Total	2,270		2,684			

	Age Standardized to 1980 U.S. Population	
	Nonsmokers	Current Cigarette Smokers
Death Rate[a]	240.9	408.0
Rate Ratio	1.0	1.7
(95% CI)	–	(1.6-1.8)
Rate Difference[a]	–	167.1
(95% CI)	–	(138.3-195.8)

[a] Death rate and rate difference per 100,000 person-years.

Key: RR = rate ratio; RD = rate difference; CI = confidence interval.

Implications for Estimating Attributable Risk

Relative risk estimates among current smokers in CPS-II have been used to estimate the number of deaths caused by cigarette smoking in the United States (U.S. Department of Health and Human Services, 1989; Shultz et al., 1991 and 1992), Latin America (U.S. Department of Health and Human Services, 1992), and many other developed countries (Peto et al., 1992 and 1994). All these applications use age-adjusted rather than age-specific RR estimates, yet the age variability observed in CPS-II is not likely to alter substantively the estimates of smoking-related deaths for several reasons.

First, these methods provide approximate rather than precise estimates of the number of deaths caused by tobacco. The estimates are necessarily crudest in countries where mortality registration is incomplete and prevalence data on smoking are limited. Methods developed by Peto and colleagues (1992 and 1994) and jointly by the Centers for Disease Control and Prevention (CDC) and the Pan-American Health Organization (U.S. Department of Health and Human Services, 1992) use lung cancer mortality to index past smoking

Table 8
Mortality from coronary heart disease as underlying cause of death among lifelong nonsmokers and current cigarette smokers: Women, Cancer Prevention Study II

	Age Specific					
	Nonsmokers		Current Cigarette Smokers			
Age	Deaths	Rate[a]	Deaths	Rate[a]	RR	RD[a]
35-39	1	2.0	0	–	–	(2.0)
40-44	5	5.9	4	8.9	1.5	3.0
45-49	8	3.8	28	27.6	7.2	23.8
50-54	25	8.1	66	45.9	5.7	37.8
55-59	84	24.3	112	76.7	3.2	52.4
60-64	211	62.0	198	162.6	2.6	100.6
65-69	353	125.7	249	307.2	2.4	181.5
70-74	523	253.5	219	478.2	1.9	224.7
75-79	717	530.1	163	846.7	1.6	316.6
80+	694	975.1	73	1,270.2	1.3	295.1
Total	2,621		1,112			

	Age Standardized to 1980 U.S. Population	
	Nonsmokers	Current Cigarette Smokers
Death Rate[a]	115.4	181.9
Rate Ratio	1.0	1.6
(95% CI)	–	(1.4-1.7)
Rate Difference[a]	–	66.5
(95% CI)	–	(48.7-84.3)

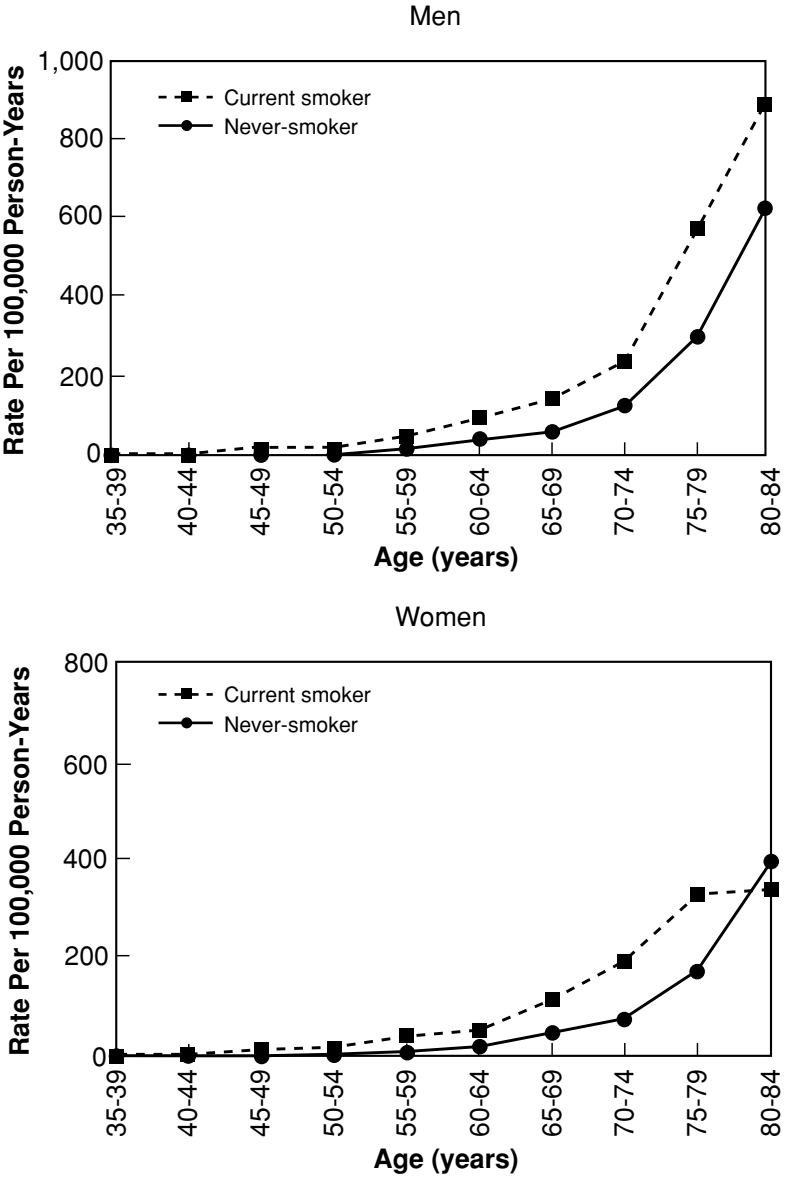
[a] Death rate and rate difference per 100,000 person-years.

Key: RR = rate ratio; RD = rate difference; CI = confidence interval.

habits. The RR values from CPS-II are adjusted, based on the death rate from lung cancer in the country of interest relative to that of nonsmokers in the United States. These evolving methods provide interim estimates, pending the availability of regional data on the prevalence of smoking and associated death rates.

The CDC's Office of Smoking and Health has assessed the effect of age variability in RR estimates on its estimates of deaths from tobacco smoking in the United States. When age-specific rather than age-adjusted RR estimates from CPS-II are included in the calculations, the attributable risk estimates decrease by approximately 10 percent in men. This decrease is similar to the difference between the CDC estimate (418,690 deaths from smoking) (Centers for Disease Control and Prevention, 1993) and the Peto and colleagues' estimate (461,000 deaths) (Peto et al., 1992 and 1994) for the United States in 1990. Both estimates are intended to be general approximations that could reasonably differ by at least 10 percent in either direction. In a recent study

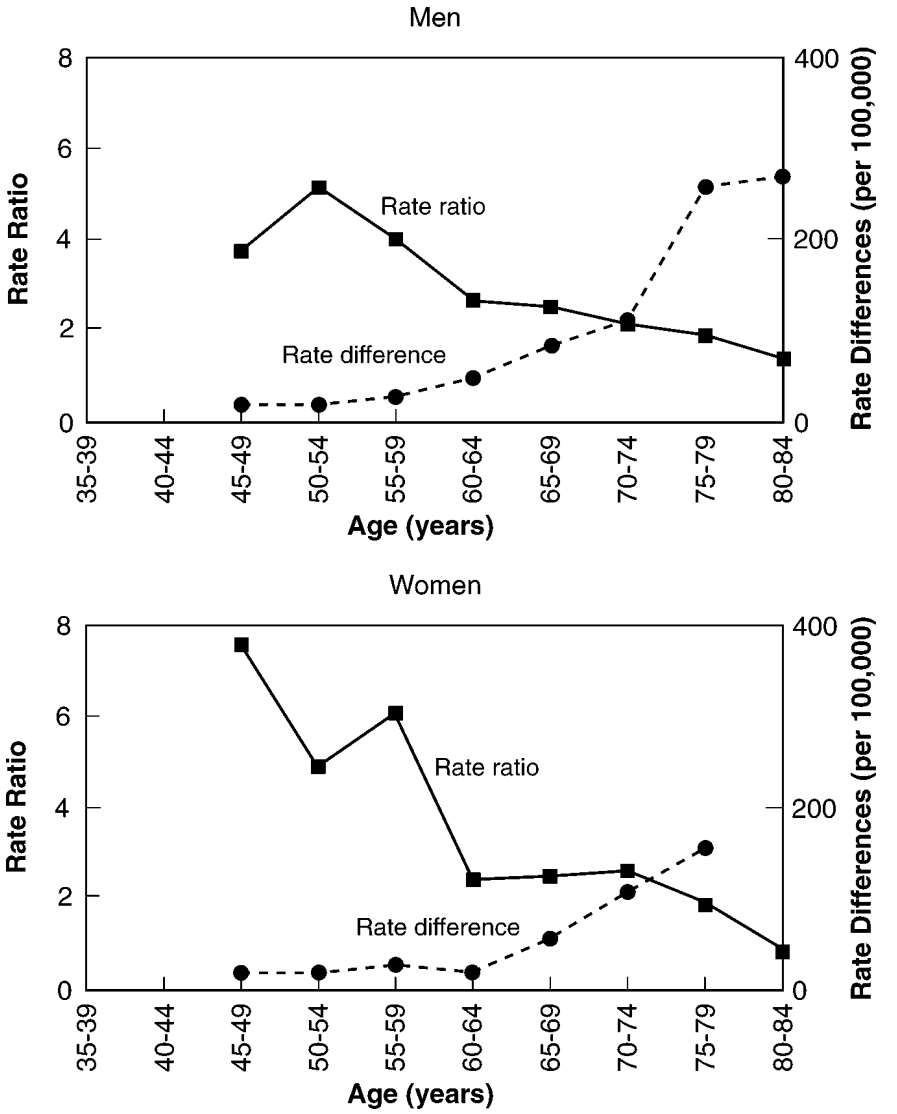
Figure 7
Stroke death rates in current cigarette smokers and lifelong nonsmokers, by age and sex



in Oregon, the CDC estimates were shown to agree well with physician reporting on death certificates (McAnulty et al., 1994).

Future refinements in the attributable risk calculations should consider stabilizing the age standard with which the RR estimates are weighted and perhaps choosing weights that resemble the age distribution of deaths from smoking-related causes. Information on years of smoking or cigarettes

Figure 8
Stroke rate ratios and rate differences in current cigarette smokers and lifelong nonsmokers, by age and sex



smoked per day probably will not improve these estimates in the near future because longitudinal information on dose is rarely available.

Age and Biological Susceptibility Our findings raise the possibility that age may increase a smoker's biological susceptibility to lung cancer, although the evidence is limited by the data available on smoking. Current cigarette consumption reported at enrollment in CPS-II may systematically underestimate past consumption among older smokers because average daily consumption decreases with age after approximately age 50 in

Table 9
Mortality from stroke as underlying cause of death among lifelong nonsmokers and current cigarette smokers: Men, Cancer Prevention Study II

	Age Specific					
	Nonsmokers		Current Cigarette Smokers			
Age	Deaths	Rate[a]	Deaths	Rate[a]	RR	RD[a]
35-39	0	0.0	2	11.9	–	11.9
40-44	1	4.5	1	4.7	–	0.2
45-49	4	6.0	14	22.3	3.8	16.3
50-54	6	4.7	28	23.7	5.1	19.0
55-59	13	9.8	49	38.8	4.0	29.0
60-64	35	28.9	83	78.7	2.7	49.8
65-69	52	50.9	91	132.3	2.6	81.4
70-74	80	111.8	83	220.0	2.0	108.2
75-79	113	280.0	81	532.8	1.9	252.8
80+	108	601.8	36	866.6	1.4	264.8
Total	412		468			

	Age Standardized to 1980 U.S. Population	
	Nonsmokers	Current Cigarette Smokers
Death Rate[a]	55.5	87.2
Rate Ratio	1.0	1.6
(95% CI)	–	(1.3-1.9)
Rate Difference[a]	–	31.7
(95% CI)	–	(17.8-45.6)

[a] Death rate and rate difference per 100,000 person-years.

Key: RR = rate ratio; RD = rate difference; CI = confidence interval.

cross-sectional surveys (Chapter 4). The broad categories by which we stratified age, years of smoking, and cigarettes smoked per day leave ample room for residual confounding. Cigarette smokers who report taking up the habit after age 30 may differ in their smoking practices, reporting patterns, or other unidentified ways from those who begin in adolescence. The absolute excess death rate from lung cancer (RD) also may differ from the RR in its relation to age or other factors.

Statistical and Methodological Implications

Even if age does not modify the carcinogenic response to cigarette smoke in a biological sense, it does affect the empirical quantitative relationships between smoking and both the RD and RR for lung cancer. One implication is that epidemiologists should consider including interaction terms between smoking and age in statistical models that consider either the RR or RD as the measure of effect. A second implication is that residual confounding by cigarette smoking should be minimized by including variables on age, years of smoking, cigarettes per day, and interaction terms when controlling for smoking in studies in which other risk factors are of primary interest. Otherwise, it will be difficult to

Table 10
Mortality from stroke as underlying cause of death among lifelong nonsmokers and current cigarette smokers: Women, Cancer Prevention Study II

	Age Specific					
	Nonsmokers		Current Cigarette Smokers			
Age	Deaths	Rate[a]	Deaths	Rate[a]	RR	RD[a]
35-39	1	2.0	1	4.0	2.0	2.0
40-44	1	1.2	3	6.7	5.7	5.5
45-49	6	2.9	22	21.7	7.5	18.8
50-54	16	5.2	36	25.0	4.9	19.8
55-59	23	6.7	58	39.7	6.0	33.0
60-64	55	16.1	50	41.1	2.5	25.0
65-69	104	37.0	78	96.2	2.6	59.2
70-74	135	65.4	81	176.9	2.7	111.5
75-79	215	159.0	61	316.9	2.0	157.9
80+	273	383.6	19	330.6	0.9	(53.0)
Total	829		409			

	Age Standardized to 1980 U.S. Population	
	Nonsmokers	Current Cigarette Smokers
Death Rate[a]	44.1	61.1
Rate Ratio	1.0	1.5
(95% CI)	–	(1.2-1.7)
Rate Difference[a]	–	17.1
(95% CI)	–	(6.9-27.2)

[a] Death rate and rate difference per 100,000 person-years.

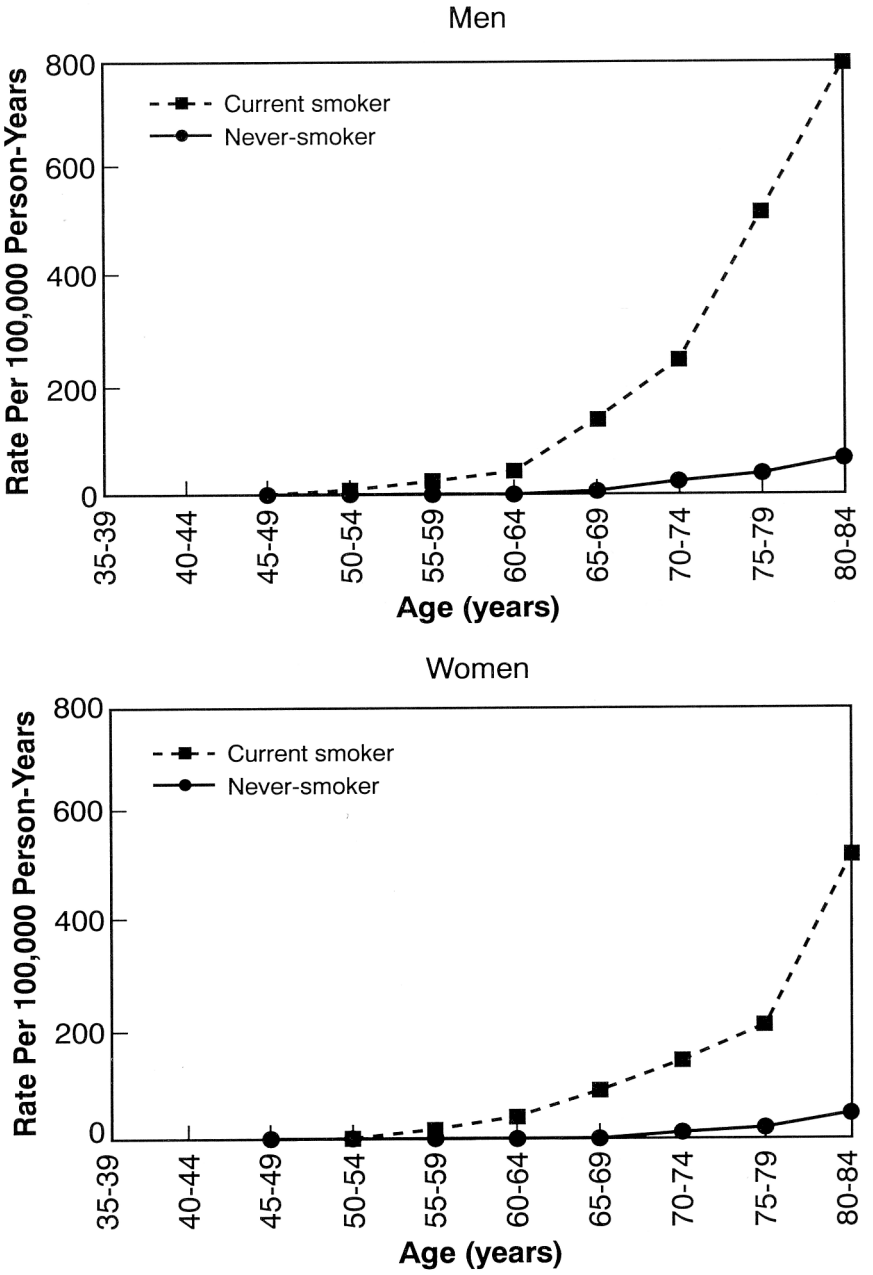
Key: RR = rate ratio; RD = rate difference; CI = confidence interval.

distinguish weak associations with occupation or nutrition, for example, from residual confounding by smoking.

CONCLUSIONS

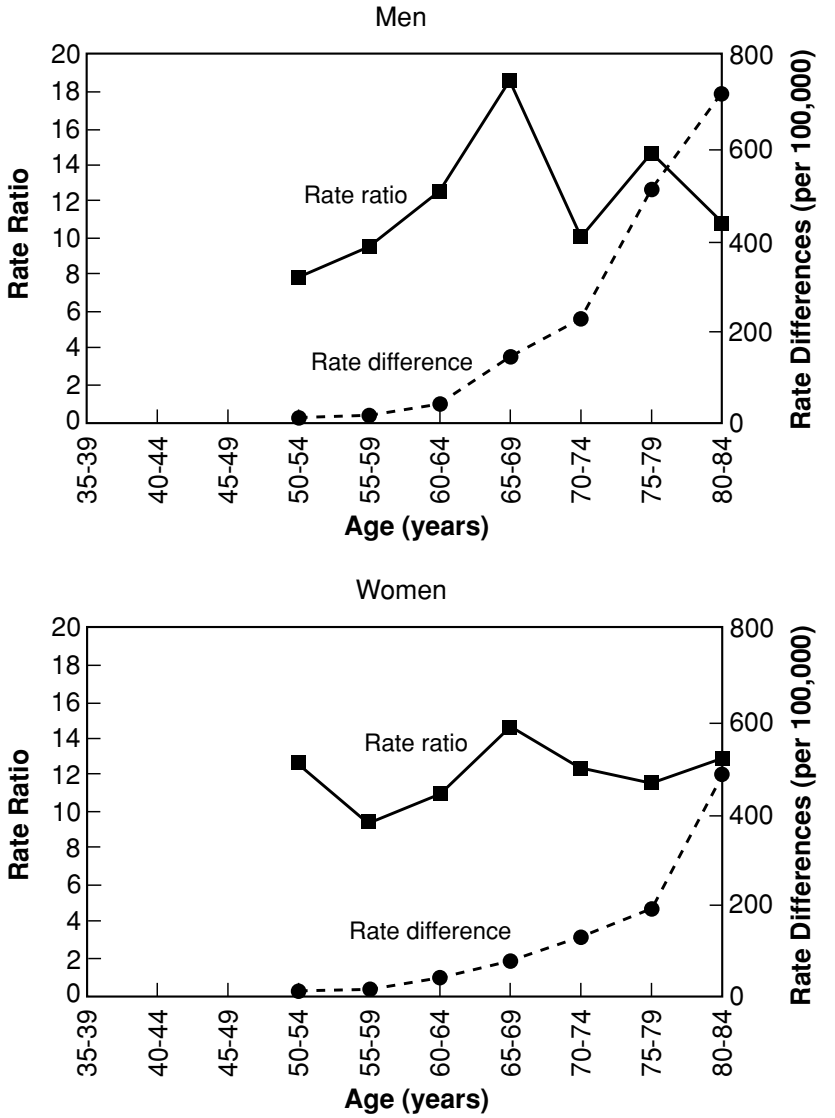
- Among current cigarette smokers in CPS-II, 52 percent of deaths from all causes in men and 43 percent in women were attributable to cigarette smoking, based on age-adjusted death rates standardized to the 1980 U.S. population.
- Cigarette smoking was strongly associated with death from lung cancer, CHD, stroke, and COPD. However, the magnitude of its adverse effect on premature mortality varied with the disease, the age and sex of the smoker, the years of smoking and daily cigarette consumption, and the epidemiologic measure used to assess risk.
- The absolute risk of dying prematurely because of cigarette smoking increased with the age of the smoker as reflected by the rising RD. Thus, the burden of risk that smoking imposes on an individual and society increases rather than decreases with the smoker's age.

Figure 9
Chronic obstructive pulmonary disease death rates in current cigarette smokers and lifelong nonsmokers, by age and sex



- In relative terms, the RR associated with cigarette smoking initially increased and then decreased with age for all the major smoking-related diseases. The initial increase reflected the time lag required for tobacco-induced injury to progress to fatal disease. The decrease

Figure 10
Chronic obstructive pulmonary disease rate ratios and rate differences in current cigarette smokers and lifelong nonsmokers, by age and sex



at older ages occurred because factors other than smoking caused a larger fraction of deaths in older than in younger smokers.

- Age-specific patterns of CHD and stroke were generally similar, as were the patterns for lung cancer and COPD. The etiologic fraction (percentage of deaths attributable to smoking) decreased more sharply with age for CHD and stroke than for lung cancer or COPD, in part reflecting the nonlinear relation between the RR and attributable risk as the RR approaches 1.0.

Table 11
Mortality from chronic obstructive pulmonary disease as underlying cause of death among lifelong nonsmokers and current cigarette smokers: Men, Cancer Prevention Study II

	Age Specific					
	Nonsmokers		Current Cigarette Smokers			
Age	Deaths	Rate[a]	Deaths	Rate[a]	RR	RD[a]
35-39	0	–	–	–	–	–
40-44	0	–	–	–	–	–
45-49	0	–	2	3.2	–	3.2
50-54	2	1.6	15	12.7	8.1	11.1
55-59	3	2.3	28	22.2	9.8	19.9
60-64	4	3.3	46	43.6	13.2	40.3
65-69	8	7.8	102	148.3	18.9	140.5
70-74	18	25.2	98	259.7	10.3	234.5
75-79	15	37.2	85	559.2	15.1	522.0
80+	13	72.4	33	794.4	11.0	722.0
Total	63		409			

	Age Standardized to 1980 U.S. Population	
	Nonsmokers	Current Cigarette Smokers
Death Rate[a]	8.5	89.9
Rate Ratio	1.0	10.6
(95% CI)	–	(7.9-14.3)
Rate Difference[a]	–	81.4
(95% CI)	–	(66.6-96.2)

[a] Death rate and rate difference per 100,000 person-years.

Key: RR = rate ratio; RD = rate difference; CI = confidence interval.

- Excess mortality from all causes of death increased with the smoker's age and the years of smoking.
- Whether or not age alters biological susceptibility to tobacco-induced lung cancer, it changes the quantitative relation between any cigarette smoking and premature death and alters the exposure-response relations of defined levels of smoking. Epidemiologists should include interaction terms between age and smoking when studying or controlling for the effect of smoking.
- The reliance on RR as the sole epidemiologic measure of association between a particular risk factor and a disease provides an incomplete picture of that disease's occurrence. Prospective studies also should examine and present death rates and RD's associated with the exposure.

Table 12
Mortality from chronic obstructive pulmonary disease as underlying cause of death among lifelong nonsmokers and current cigarette smokers: Women, Cancer Prevention Study II

	Age Specific					
	Nonsmokers		Current Cigarette Smokers			
Age	Deaths	Rate[a]	Deaths	Rate[a]	RR	RD[a]
35-39	0	–	0	–	–	–
40-44	0	–	0	–	–	–
45-49	0	–	2	2.0	–	2.0
50-54	2	0.6	12	8.3	12.9	7.7
55-59	6	1.7	24	16.4	9.5	14.7
60-64	11	3.2	44	36.1	11.2	32.9
65-69	16	5.7	68	83.9	14.7	78.2
70-74	24	11.6	65	141.9	12.2	130.3
75-79	24	17.7	39	202.6	11.4	184.9
80+	29	40.7	30	522.0	12.8	481.3
Total	112		284			

	Age Standardized to 1980 U.S. Population	
	Nonsmokers	Current Cigarette Smokers
Death Rate[a]	4.2	56.8
Rate Ratio	1.0	13.4
(95% CI)	–	(10.5-17.2)
Rate Difference[a]	–	52.6
(95% CI)	–	(42.1-63.0)

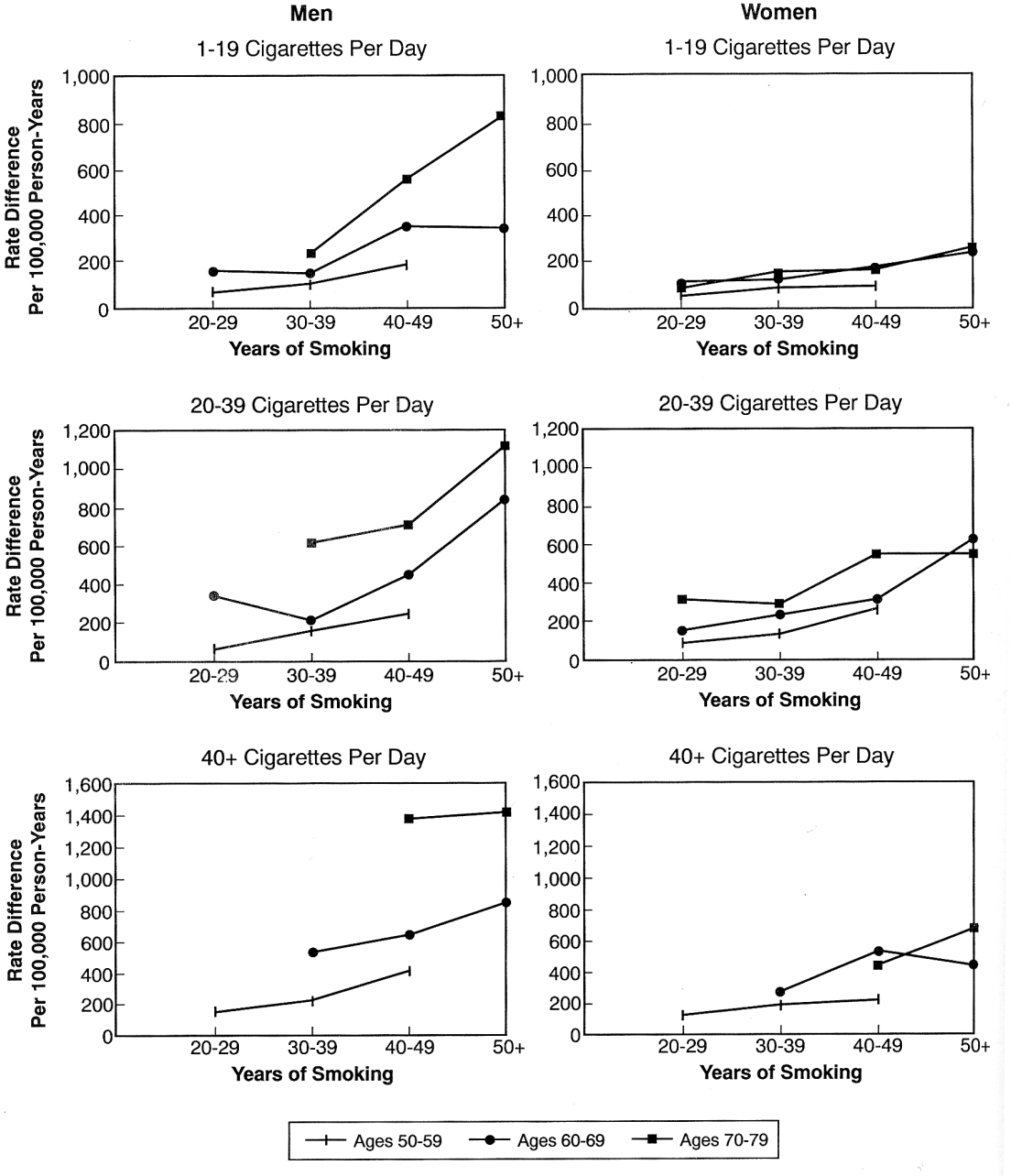
[a] Death rate and rate difference per 100,000 person-years.

Key: RR = rate ratio; RD = rate difference; CI = confidence interval.

- Programs that prevent young people from starting smoking and enable those who already smoke to quit by middle age would have the greatest short- and long-term impact on the tobacco epidemic.

Figure 11

Excess death rates (RD) from lung cancer, by age, years of smoking, and cigarettes per day—Cancer Prevention Study II: Duration fixed at time of enrollment[a]



[a] Graphs portray only positive RD values based on cells containing three or more deaths in smokers and never-smokers.

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