TABLE 4.—Continued

Reference	Population	Intervention	Outcome	Cases among former smokers	Overall effect of intervention	Effect of smoking cessation (nonrandomized)
Rose, Tunstall-Pedoe, Heller (1983)	12 pairs of factories in UK, 18,210 men aged 40–59	Diet, antismoking, hypertension control	Nonfatal MI and CHD deaths	403	4% net reduction in prevalence of current smoking, virtually no difference in outcome between the two groups	No specific analysis of ex-smokers
Rose et al. (1982)	1,445 healthy British civil servants all smoking at high CHD risk	Antismoking advice	CHD deaths	49	19% reduction in intervention group	19% CHD reduction in group offered antismoking advice, not statistically significant
Wilhelmsen et al. (1986)	10,004 random Göteborg men aged 45–55	Antihypertensive, dietary, antismoking advice	Major CHD	NR	No difference	Intervention achieved only small differences between the groups for smoking and other risk factors

NOTE: CHD=coronary heart disease; MRFIT=Multiple Risk Factor Intervention Trial; MI=myocardial infarction; NR=not reported.

The Multiple Risk Factor Intervention Trial (MRFIT) was designed to test whether reduction of diastolic blood pressure, serum cholesterol, and cigarette smoking decreases the incidence of CHD (Hughes et al. 1981; MRFIT Research Group 1986; Grimm 1986). Men aged 35 to 57 were screened; of those in the upper 15 percent of CHD risk (based on coefficients from the Framingham Study), but without overt CHD, 6,428 were randomized to special intervention, and 6,438 were assigned to usual care. Men in the special intervention group were given intensive instructions concerning diet and smoking cessation and were treated for hypertension. Those in the usual care group were referred to their regular source of medical care. The difference in total cholesterol between the two groups was only half that expected; because of better than anticipated hypertension treatment in the usual care group, the difference in blood pressure was also substantially less than expected. At the outset, 59 percent of the participants were current cigarette smokers. After 12 months, 31 percent of the smokers in the intervention group had quit (verified by thiocyanate (SCN^-) levels) compared with 12 percent of the smokers in the control group. At the end of the 6-year trial, 46 percent of smokers in the intervention group had quit compared with 29 percent in the control group. Mortality resulting from CHD was only 7 percent lower in the special care group, a difference that did not approach statistical significance. The authors suggested that the small decrease in risk was due in part to the smaller than anticipated differences in risk factor levels between the two groups and that some of the benefit in risk factor reduction might possibly have been counterbalanced by an unfavorable response to antihypertensive therapy in some of the hypertensive patients (MRFIT Research Group 1982). Within the intervention group, those who quit in the first year had a multivariate-adjusted relative risk 50 percent lower than that of persistent smokers; in the control group, adjusted relative risk 30 percent lower than that of persistent smokers. In this trial, risk of sudden CHD death was reduced 65 percent among quitters compared with persistent smokers. Because all participants were seen at least annually, the possible misclassification of smoking status was minimized.

The 10.5-year followup data from MRFIT have recently been published (MRFIT Research Group 1990). Deaths due to CHD were 10.6 percent lower in the special intervention group (95-percent CI,–23.7 to 4.9) compared with the usual care group (two-sided p value=0.24). This reduction in risk was largely attributable to a 24.3-percent lower risk of death due to acute MI (2-sided p value=0.04). Total cardiovascular mortality was 7.1 percent lower after 10.5 years in the special intervention group compared with the usual care group ($p>0.05$). In one analysis not based on randomized groups, CHD mortality rates of smokers who had quit within the first 12 months of the trial and of those who were still smoking at that time were compared (Ockene et al. 1990). Quitters had a 37-percent reduction in mortality. After adjustment for other CHD risk factors, the reduction was 42 percent (95-percent CI, 16–60). The slightly greater benefit observed after adjustment for risk factors indicates that there was little confounding and that it was in the direction that would tend to underestimate the benefit of cessation. This analysis ignored any changes in smoking status after the first annual examination. To the extent that either some of the quitters resumed smoking or some of the current smokers quit, that analysis would yield an underestimate of the benefits of cessation. A second analysis compared quitters who remained abstinent at the first

three annual examinations with persistent smokers. In this analysis, which would be affected to a lesser extent by misclassification, former smokers had a 65-percent reduction in risk compared with persistent smokers (95-percent CI, 37–80).

A trial using a somewhat similar design was conducted in Oslo, Norway (Hjermann et al. 1981; Hjermann, Holme, Leren 1986). Males aged 40 to 49 were screened for coronary risk, and normotensive men at high risk of CHD due to elevated serum cholesterol, smoking, and other risk factors were identified. The participants had no clinical CHD at the time of randomization to the intervention or control group (N=604 and N=628, respectively). The intervention consisted of advice and instruction on altering diet and reducing smoking. Participants were examined at least annually during the 5 years of followup. After 5 years, fatal and nonfatal CHD was reduced in the interventiongroup by 47 percent. There was greater success in reducing cholesterol in this trial than in inducing smoking cessation. The mean serum cholesterol was approximately 13 percent lower in the intervention group than among the controls. However, only 25 percent of the smokers in the intervention group and 17 percent in the control group quit entirely, although many reduced the amount smoked. There was an inverse relation between CHD incidence and percentage change in tobacco consumption, but this did not attain statistical significance. The authors calculated that approximately 25 percent of the difference in CHD incidence between the two groups was attributable to differences in smoking.

A second report (Hjermann, Holme, Leren et al. 1986) included followup through 102 months. Statistically significant reductions among the intervention group compared with the control group were seen for fatal coronary events (reduced 59 percent), total coronary events (reduced 44 percent), and total cardiovascular events (reduced 61 percent).

The World Health Organization European Collaborative Trial in the multifactorial prevention of CHD was conducted at several sites in Europe. Pooled results were reported from centers in the United Kingdom, Belgium, Italy, and Poland (WHO European Collaborative Group 1983); separate reports have also been published from centers in the United Kingdom (Rose, Tunstall-Pedoe, Heller 1983) and Belgium (Kornitzer et al. 1983). A total of 66 factories involving 49,781 men were randomized to a multifactorial risk factor reduction program or to the control group. The reduction of levels of risk factors varied considerably among the centers. Overall, the reduction in risk factor levels was modest, and there was no significant decline in CHD endpoints in the intervention group. The effect on CHD was broadly correlated with changes in risk factors. There was no specific analysis on the impact of smoking cessation.

The Belgian center was the largest in the European Collaborative Trial. Fifteen pairs of factories were randomly allocated to the intervention or control groups, which included 19,409 men aged 40 to 59 years. The intervention included advice about smoking cessation and reduction of hypertension and elevated cholesterol. Subjects were screened as part of the trial, but referred to their own physicians for therapy. After 6 years, there was a 24.5-percent reduction in fatal and nonfatal CHD in the intervention group compared with the control group (p=0.03) (Kornitzer et al. 1983). The rates in the intervention and control groups continued to diverge throughout the followup

period. No specific analysis was conducted to assess the independent effect of smoking cessation on risk of CHD.

The multifactor primary prevention trial in Göteborg, Sweden focused on reduction of hypertension, elevated serum cholesterol, and smoking (Wilhelmsen et al. 1986). A random sample of 10,004 men aged 45 to 55 years was included in the intervention group, and 2 other random samples of the same size were identified as controls. Of those invited to participate in the intervention group, 7,495 attended the first screening examination. At the outset, within the intervention and control groups combined, 20.6 percent were former smokers. After 4 years, the proportion of former smokers increased to 27.7 percent, and after 10 years to 39.4 percent in the intervention group. In the control group, the percentage of former smokers also increased—to 22.3 percent at 4 years and to 36.1 percent at 10 years. The differences achieved for other risk factors between the intervention and control groups were also quite small. After 10 years, there were virtually no differences in fatal and nonfatal outcomes between the groups.

The center in the United Kingdom was also large (Rose, Tunstall-Pedoe, Heller 1983), with 12 pairs of factories and 18,210 men aged 40 to 59 years. There were only very modest changes in risk factors other than cigarette smoking. The reported number of cigarettes smoked per day in the intervention group decreased by 16 percent, but the proportion of current cigarette smokers decreased by only 4 percent. Rose and Hamilton (1978) stated that whereas self-report of cessation is likely to be reasonably accurate, reported decreases in smoking are probably exaggerated. With such small net changes in risk factors, it is not surprising that there was virtually no difference in the rate of CHD between the two groups.

Only one trial has attempted to assess the effect of advice for smoking cessation without intervening for other risk factors simultaneously. In theory, trials of this design can provide the clearest indication of the effect of such advice in the absence of other effects. Participants were selected from a cohort of 16,016 from the Whitehall Civil Servants Study (Fuller et al. 1983). From this group, 1,445 high-risk male smokers aged 40 to 59 were randomized to a normal care group or the intervention group that received antismoking advice. At year one, 51 percent of the intervention group reported that they were not smoking, and at year three, 36 percent reported the same. In the normal care group, the corresponding percentages were 10 and 14 percent. A third of the quitters reported smoking cigars or a pipe. It is important to note that the questionnaire response rate at 3 years was 64 percent in the intervention group and 70 percent in the normal care group (Rose and Hamilton 1978). The 9-year response rate was 83 percent. At that point, 55 percent of responders in the intervention group reported quitting, as did 41 percent in the normal care group. Despite the similarity of smoking prevalence of the two groups, at 10 years CHD mortality decreased by 18 percent in the intervention group. This difference did not attain statistical significance (95-percent CI, –43 to +18 percent) (Rose et al. 1982).

Smoking Cessation and CHD Risk Among Persons With Diagnosed CHD

Studies examining smoking cessation and CHD risk among persons with diagnosed CHD may be less prone to some of the methodologic pitfalls discussed in Chapter 2.

In many instances, studies are primarily of individuals who were smokers up to the time of the infarction. Such a major health event can be a powerful motivation to quit smoking permanently. Moreover, the timing of quitting often coincides with the infarction and is therefore ascertained quite accurately. Because those with a prior diagnosis of CHD are at such high risk for another event, the estimates of effect can be relatively precise, even with a modest number of individuals under study. One difficulty in interpreting these studies is in the comparison of quitters with never smokers. Never smokers who suffer MI tend to have a worse CHD risk factor profile (apart from smoking) than smokers (Mulcahy 1983). However, most of the other risk factors are less amenable to change than smoking. After smoking is removed as a risk factor among former smokers, the effect is often a better prognosis than that for never smokers. Several of these issues and a review of the literature prior to 1983 are discussed by Mulcahy (1983). This researcher found that studies were quite consistent in showing that quitters had about half the risk of recurrent MI or CHD death compared with persistent smokers (Mulcahy 1983). Nearly all studies of this issue have indicated a benefit of cessation (Table 5).

A cohort of 213 patients who survived for 28 days a first attack of coronary insufficiency or MI was studied for 5 years (Mulcahy et al. 1977). Of these, 190 were smokers at the time of the event. Of the 89 who stopped, the cumulative 5-year death rate was 14.6 percent. Of the 42 who reduced cigarette use, the rate was 14.2 percent. However, among the 59 persistent smokers, 28.8 percent died within 5 years. Nearly all of the deaths were associated with CHD.

This study was extended by further accrual of patients and followup of 551 men less than 60 years of age (Daly et al. 1987). Of the 406 current smokers at the time of the event, 140 had stopped by year two. Those quitters had a 10-percent reduction in risk of sudden death and a 40-percent reduction in risk of total mortality compared with those who continued to smoke.

A 1978 report from the Framingham Study (Sparrow, Dawber, Colton 1978) compared the survival of 56 individuals who quit smoking after a first MI with 139 who continued to smoke after the diagnosis. Within 2 to 3 years after diagnosis, former smokers had a significantly better survival rate than persistent smokers. The 6-year mortality rate (estimated by life table methods) was 18.8 percent among quitters compared with 30.4 percent among persistent smokers. When the risk of recurrent MI was assessed, the authors found that former smokers had a lower risk than persistent smokers, with a 6-year reinfarction rate of 15.5 percent in quitters versus 21.5 percent among smokers. However, with only eight reinfarctions among the quitters, the differences were not statistically significant. The rate of decline in risk could not be assessed because of the small samples.

Framingham Study investigators (Hubert, Holford, Kannel 1982) conducted a long-term followup study of 130 subjects with angina pectoris. They found that smoking status at the examination ascertaining angina was modestly associated with subsequent risk of a later, more serious CHD outcome. Apparently, the change in smoking behavior explained this finding. Of the angina patients who smoked, 14 percent quit between the onset of disease and the biennial examination when the diagnosis was confirmed. Another 29 percent quit during the followup period. In this cohort, the heavier smokers

TABLE 5.—Studies of the effect of smoking cessation on persons with diagnosed CHD

Reference	Population	Followup	Cases among former smokers	Reduction in risk compared with persistent smokers[a]	Comments
Mulcahy et al. (1977)	190 Dublin men aged <60 who smoked at time of first coronary insufficiency or MI	5 yr	13 deaths	50%	Smokers (N=42) who reduced cig/day also had a lower mortality compared with persistent smokers
Daly et al. (1987)	373 men aged <60 who smoked at time of first MI or unstable angina and survived 2 yr	Average 9.4 yr; ≤16 yr	NR	10% for sudden death; 40% for total mortality	No further classification of smoking; some of same patients as in Daly 1983
Sparrow, Dawber, and Colton (1978)	Framingham Heart Study: 195 cohort members who smoked at time of first MI	6 yr	10 deaths	40%	
Hubert, Holford, Kannell (1982)	Framingham Heart Study: subjects with angina	≤26 yr	NR	10-yr followup: <60 yr 90% ≥60 yr 60% 26-yr followup: <60 yr 70% ≥60 yr 10%	Only 25 cases in baseline smokers, so estimates are statistically unstable
Salonen (1980)	North Karelia, Finland: 523 men aged <65 who smoked at first MI	3 yr	26 deaths; 22 CHD deaths	40% (60–10) 40% (60–0)	Followup began 6 mo after MI; apparent benefit more pronounced in first 6 mo of followup (60%)

TABLE 5.—Continued

Reference	Population	Followup	Cases among former smokers	Reduction in risk compared with persistent smokers[a]	Comments
Von der Lippe and Lund-Johansen (1982)	1,330 participants in the Norwegian timolol trial who smoked at time of MI	17 mo	31 deaths in those who stopped smoking before entering the trial	None	Study not designed to examine effects of smoking cessation; no details provided on possible confounding
			37 deaths in those who stopped in the first months of the trial	10%	
Rønnevik, Gunderson, Abrahamsen (1985)	1,330 participants in the Norwegian timolol trial who smoked at time of MI	17 mo	44 recurrent nonfatal MI	33% reduction; 8% in quitters, 12% in persistent smokers	
Shapiro, Howat, Singh (1982)	142 MI survivors aged <45	≤10 yr	NR	80% (former and never smokers vs. persistent smokers)	Former and never smokers considered together, not separately
Aberg et al. (1983)	983 Göteborg male smokers at time of MI	≤10.5 yr	104 recurrent nonfatal MI; 80 CHD deaths	30%; difference between groups increased with time	30% quitters had worse predicted prognosis at baseline; no further assessment of smoking beyond 3 mo after initial MI
Daly et al. (1983)	374 Dublin men, smokers at time of MI diagnosis or angina	Mean 7.4 yr, ≤13 yr	80 deaths	60% overall; 40% first 6 yr; 80% 7–13 yr	Followup began 2 yr after MI, when smoking status was assessed

TABLE 5.—Continued

Reference	Population	Followup	Cases among former smokers	Reduction in risk compared with persistent smokers[a]	Comments
Johansson et al. (1985)	156 Göteborg women aged ≤65, smokers at time of first MI	5 yr	12 deaths	60% (80–20)	Quitters had worse baseline prognosis; differences between groups were apparent early and increased with time
Perkins and Dick (1985)	119 UK patients who smoked at first MI	5 yr	9 deaths	60%	
Vlietstra et al. (1986)	11,605 patients in CASS who smoked at time CHD was diagnosed by angiography	5 yr	By risk quartile: (best) 1: 13 2: 21 3: 44 (worst) 4: 156 overall: 234	Total mortality: 40% 40% 50% 20% 40% (50–20)	Quitters had worse baseline prognosis; exclusion of those with mixed smoking behavior and close followup reduced likelihood of misclassification of exposure; also, hospitalization for MI was substantially reduced in former smokers
Hermanson et al. (1988)	3,045 CASS patients with CHD aged 35–54	5.3 yr for MI or death	35–54 yr: NR	40% (50–30)	Reanalysis of a subset of patients analyzed by Vlietstra (1986)
	1,893 CASS patients with CHD aged ≥55		55–59 yr: 99 60–64 yr: 92 65–69 yr: 48 >70 yr: 29	30% (50–20) 30% (50–10) 30% (60–0) 70% (80–30)	

TABLE 5.—Continued

Reference	Population	Followup	Cases among former smokers	Reduction in risk compared with persistent smokers[a]	Comments
Hallstrom, Cobb, Ray (1986)	310 survivors of out of hospital arrest, smokers at that time	Mean 47.5 mo		35% for fatal recurrent cardiac arrest	Borderline statistical significance
Green (1987)	2,199 men who smoked at time of MI	2 yr	NR	30% for CHD	
Hedback and Perk (1987)	157 smokers at time of MI	5 yr	13 fatal and nonfatal CHD	50%	Trial of rehabilitation including smoking cessation
Galan et al. (1988)	160 patients re-angiographed after angioplasty	Mean 7 mo		31% decreased for restenosis	Groups were similar at baseline
Phillips et al. (1988)	530 male British former smokers with non-MI CHD	Mean 7.5 yr		33% for fatal or nonfatal CHD	No update of smoking data; no assessment of severity of baseline CHD
	175 former smokers with MI, aged 40–59			10%	
Goldberg, Szklo, Chandra (1981)	325 post-MI patients	≤10 yr		Survival: Quit at MI / Not quit 1 yr: 99% / 98% 5 yr: 97% / 84% 10 yr: 95% / 51%	Independent of multiple risk factors; no update of smoking status

NOTE: CHD=coronary heart disease; MI=myocardial infarction; NR=not reported; CASS=Coronary Artery Surgery Study.
[a]95% confidence interval shown in parentheses when available.

were more likely to quit than the lighter smokers. Former smokers had a lower rate of subsequent CHD. There was a suggestion that older persons benefited less; however, this finding could not be confirmed because only a small fraction of the 25 older smokers actually quit.

Salonen (1980) monitored a Finnish cohort of men less than 65 years of age whose smoking behavior was assessed 6 months after MI. Of these, 352 were never smokers, 302 were persistent smokers, and 221 quit smoking within 6 months after MI. Three years after MI, quitters had a 40-percent reduction in risk of total mortality (95-percent CI, 10–60 percent) and of CHD death (95-percent CI, 10–60 percent) compared with persistent smokers. The reduction in risk was more pronounced in earlier periods; between 6 months and 1 year, mortality was reduced by 60 percent (95-percent CI, 10–80 percent). It is possible that the apparent decline in benefit may represent misclassification because current smokers continued to quit but were still analyzed as current smokers. The benefits of quitting were strongest among those with the best prognosis after infarction. Of post-MI deaths, 28 percent were estimated to be attributable to continued smoking.

As part of the Norwegian trial of timolol use after MI, mortality of the 1,884 participants was ascertained over an average of 17 months according to smoking status. Virtually no differences were observed (Von der Lippe and Lund-Johansen 1982). Across both the timolol and placebo groups, 8 percent of the nonsmokers died, compared with 8 percent of those who stopped smoking before entry into the trial, 7 percent among those who quit in the first month of the trial, and 8 percent among persistent smokers. However, there was a reduction in reinfarctions, 8 percent among those who quit in the first month of the trial compared with 12 percent among persistent smokers (Rønnevik, Gundersen, Abrahamsen 1985).

Shapiro, Howat, and Singh (1982) monitored 142 patients who survived a first MI that occurred when the patient was younger than age 45. Of these patients, 50 who continued to smoke more than 20 cigarettes per day had substantially higher mortality rates (58-percent 10-year mortality by life table methods) than did the 61 never and former smokers (12-percent mortality). The survival curves began to diverge 1 year after MI. Unfortunately, data were not presented separately for former smokers, and apparently there were only a small number of never smokers.

Aberg and colleagues (1983) studied 983 men aged 67 years or less who were listed in the MI Register of Göteborg between 1968 and 1977. The men were smokers within 3 months of their initial MI, who survived hospitalization. Not all men listed in the Register were included in the study, but the selection process did not introduce bias. Quitting was defined as not smoking 3 months after the infarction. Followup began at that point and continued for 10.5 years. The 542 males who had stopped smoking by 3 months after infarction had a significantly worse prognosis, based on predischarge characteristics, than did the 441 persistent smokers. Those who quit had substantially more left ventricular failure and higher peak enzyme levels during hospitalization. Based on these and other preinfarction and hospitalization variables, those who quit had a predicted 2-year mortality that was 8 to 9 percent higher than that of persistent smokers. However, despite this slightly worse baseline prognosis, quitters had a significantly lower mortality than did persistent smokers. Overall, the 5-year mortality

was significantly reduced among quitters, with a cumulative mortality rate 30 percent lower. The effect was somewhat stronger among those aged 50 or older than among younger men, but was significant in both age groups. The cumulative 5-year reduction in recurrence of MI was 30 percent. These estimates almost certainly underrepresent te true effect of cessation for two reasons: quitters at baseline had a distinctly worse prognosis, and smoking cessation was defined only at the point 3 months after infarction. It is likely that some of the smokers quit at a later point; this would tend to dilute the smoking group with ex-smokers who enjoy a lower risk. Thus, the rates of mortality and reinfarction among truly persistent smokers would be underestimated in this study. The two groups began to diverge for both endpoints after as little as 1 year postinfarction, and the differences increased with time. This report confirmed and extended initial findings from that study (Wilhelmsson et al. 1975).

Several studies have monitored patients with angiographically diagnosed coronary disease. Kramer and coworkers (1983) studied 278 men with sequential coronary angiograms. These researchers found that neither cigarette smoking at the initial or followup examination nor smoking cessation was predictive of progression of atherosclerosis.

Daly and colleagues (1983) studied 217 men who stopped smoking after a first diagnosis of unstable angina or MI and 157 persistent smokers. Smoking status was defined 2 years after the first diagnosis. As in the Aberg study (1983), those who quit tended to have a more serious diagnosis than the persistent smokers. However, quitters enjoyed substantial protection compared with persistent smokers. For total mortality, risk was reduced by 60 percent among those who quit smoking compared with continuing smokers; for fatal reinfarction, risk was also reduced by 60 percent. During the first 6 years of followup, the reduction in risk was 40 percent (95-percent CI, 10–60 percent), but in the followup period of 7 to 13 years, the benefits of quitting were more marked, with a reduction in risk of 80 percent (95-percent CI, 50–90 percent). The benefits of quitting were more marked among those with less severe initial disease. In this study, quitters had a lower cumulative mortality than did never smokers with these diagnoses. Those never smokers may have had more coronary risk factors other than smoking which may be less amenable to change than smoking.

In a later study with some of the same patients, Daly and coworkers (1985) found that 1 year after the initial event, 241 quitters had a 40-percent lower prevalence of angina compared with 143 persistent smokers. However, by 6 years of followup, the prevalence of angina was the same in both groups and remained similar throughout the followup period of 17 years. Green (1985) noted that the prevalence of angina 6 months after infarction among 851 ex-smokers was equivalent to that among smokers. However, it is unclear whether the ex-smokers were smoking at the time of the event.

Most studies of the effect of post-MI cessation have been conducted among men. Johansson and colleagues (1985) examined 156 women in Göteberg, younger than 65, who were smokers at the time of their first MI. The definitions and criteria were the same as those in the study by Aberg and coworkers (1983). Three months after infarction, 75 women continued to smoke and 81 had stopped. As in the Göteberg Study of men (Aberg et al. 1983), women who quit had more severe infarctions. Despite the worse prognosis normally associated with the higher enzyme elevations and other

indications of severity, the quitters had a significantly better survival. The reduction in risk compared with smokers remained at 60 percent (95-percent CI, 20–80 percent), and after adjustment for prognostic features before and during the infarction, the reduction remained at 60 percent. When compared with never smokers, the relative risk among quitters was 1.1. The reinfarction rate was slightly, though not significantly, higher among persistent smokers.

Similar findings for a rapid benefit were observed in the small study of Perkins and Dick (1985). For 5 years, these researchers monitored 52 patients (including 11 women) who stopped smoking at the time of the infarction and 67 persistent smokers (of whom 18 were women). Men who quit had a 50-percent reduced risk of death; for women it was 60 percent lower.

As part of the Coronary Artery Surgery Study, the effect of smoking cessation on risk of clinical CHD outcomes was assessed in men with documented coronary atherosclerosis by angiography (Vlietstra et al. 1986). The death rates among 1,490 quitters were compared with those of 2,675 persistent smokers and 2,912 never smokers. Men who were quitters at baseline but who subsequently resumed smoking and those who were smokers initially but later stopped were excluded from the analysis. Hence, this study was largely free of misclassification. As in most of the other studies, the quitters had slightly worse prognoses than did the persistent smokers. At every level of risk, however, quitters had a significantly better 5-year survival. Overall, the reduction in risk (from Cox regression) was 40 percent (95-percent CI, 20–50 percent). The benefit was slightly more pronounced among those with the worst baseline prognosis. Overall, the 5-year survival rate among quitters was similar to that of never smokers (85 vs. 87 percent, respectively). Nearly all the benefit was attributable to a decreased rate of CHD death. After adjustment for prognostic score, the rate of hospitalization for MI was substantially higher among persistent smokers than among quitters (11.3 vs. 7.1 percent, respectively). For both fatal and nonfatal endpoints, the rates began to diverge substantially after about 1 year (Figure 6). Because of the careful study design and the unusually large number of cases, the results of this study must be accorded considerable weight.

In an extension of the analysis of survival data from the Coronary Artery Surgery Study, the effects of smoking cessation were examined in a population of individuals aged 55 and older with angiographically documented coronary disease (Hermanson et al. 1988). As in the previous report, persistent smokers were defined as those 1,086 smokers who did not quit throughout the 6-year followup period, and quitters were those 807 who stopped smoking 1 year before the baseline angiogram and who did not resume smoking during followup. The experience of 3,045 younger subjects aged 35 to 54 years was also examined. At every age, quitters had better survival rates than did persistent smokers, and there was no evidence that the benefit was attenuated with increasing age.

Employing a different approach, Hallstrom, Cobb, and Ray (1986) studied a cohort of 310 men who smoked and were discharged from the hospital after an episode of out-of-hospital cardiac arrest. After the arrest, 219 men continued to smoke and 91 men quit. During the average 47.5 months of followup, 67 persistent smokers and 18 former smokers died of a recurrent cardiac arrest. After adjustment across baseline risk

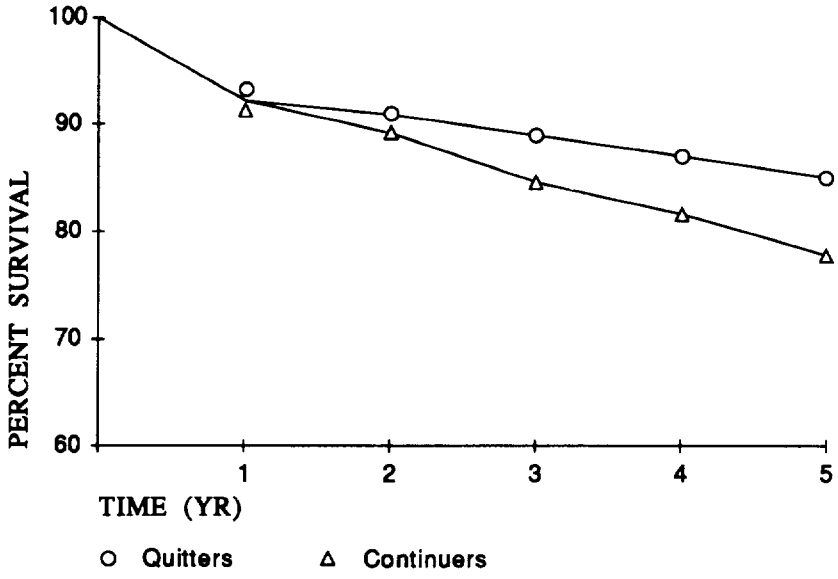

FIGURE 6.—Effect of smoking cessation on survival among men with documented coronary atherosclerosis; pooled survival among quitters (○) (N=1,490) and continuers (Δ) (N=2,675)

SOURCE: Vlietstra et al. (1986).

strata, this difference was of borderline significance in a life table analysis (p=0.076). After exclusion of crossovers (14 smokers quit ≥6 months after the arrest, and 2 quitters resumed smoking), the benefit of cessation was slightly more pronounced (p=0.048).

Analysis of data from a trial of practolol also provided information on the effects of smoking cessation after MI (Green 1987). There were 855 never smokers, 1,344 persistent smokers, and 851 individuals who quit smoking after the entry MI. Those who stopped smoking had a worse outcome initially than persistent smokers, and the benefit from cessation did not appear until 2 years after the event. When events in the first 6 weeks after the index MI were excluded, the benefits of cessation appeared at about 18 months. By 24 months, those who stopped had a 30-percent CHD risk reduction. As in other studies, former smokers when compared with continuing smokers tended to have more severe MI, with significantly more pulmonary congestion noted when x-rayed and significantly greater occurrence of faster dysrhythmia. This supports the view that those with a worse MI are more likely to quit, and it explains why quitters in the study had a worse initial outcome.

In a trial of rehabilitation after MI, 147 patients in a Swedish hospital were routinely invited to participate in a rehabilitation program; 158 patients in a comparable hospital were not (Hedback and Perk 1987). The cardiovascular experience in the intervention

group was favorable, and when the specific effect of smoking cessation was examined among the 82 patients from both groups who quit after MI, approximately 15.9 percent died in the subsequent 5 years compared with 30.6 percent among the persistent smokers and 11.8 percent among the never smokers.

The influence of smoking cessation on frequency of restenosis after coronary angioplasty was assessed by comparing 84 persistent smokers with 76 individuals who stopped at the time of angioplasty (Galan et al. 1988). Patients were reexamined angiographically after an average of 7 months. Restenosis was significantly higher in persistent smokers (55 vs. 38 percent, p=0.03). Several other studies (Fleck et al. 1988; Vandormael et al. 1987) failed to find an association between smoking at angioplasty and subsequent restenosis, but those studies did not consider the impact of cessation at the time of angioplasty. Although the mechanisms of restenosis are not clear, the findings of Galan and coworkers (1988) are consistent with a fairly rapidly acting process for decreased risk after cessation.

As part of the British Regional Heart Study described above, investigators also monitored 1,515 men with evidence of CHD but without MI and 428 men with evidence of prior MI at entry (Phillips et al. 1988). Smoking behavior was assessed at baseline, and the men, aged 40 to 59, were studied for an average of 7.5 years. There was no update of the smoking information. After adjustment for age and other risk factors, for those with non-MI CHD at baseline, the relative risk comparing former with never smokers was 1.4; for current smokers, it was 2.1. For those with a history of MI, the relative risk for former smokers was 1.7; and for current smokers, it was 1.9. The degree of misclassification that may have occurred during the followup period is difficult to assess. No information is available on the duration of abstinence or the degree of severity of CHD as distributed by smoking status.

In a community-based followup of 325 post-MI patients in Baltimore, MD, Goldberg, Szklo, and Chandra (1981) found that after control for several clinical and sociodemographic factors, survival among those who quit at the time of MI was substantially improved. The 1-, 5-, and 10-year survival rates among those who quit were 99, 97, and 95 percent, respectively; in contrast, the rates among persistent smokers were 98, 84, and 51 percent, respectively. Despite the lack of updates on smoking behavior, there was a trend for diverging survival between the two groups.

Summary of Smoking Cessation and CHD Risk

Within the past 40 years, large amounts of data regarding the effect of smoking cessation on CHD risk have been accumulated from numerous studies. However diverse in design and location, these studies consistently find that the risk of CHD is reduced among former smokers compared with those who continued to smoke. The data are compatible with a rapid, partial decline in risk, followed by a more gradual decline reaching levels of never smokers after a prolonged period. The initial decline appears to occur within 1 year of cessation or perhaps even less and constitutes a reduction of about one-half or more of the excess risk associated with current smoking. The remaining decline in excess risk is more gradual, with the risks reaching those of never smokers only after a number of years of smoking abstinence. This pattern of

decline in excess risk is compatible with multiple effects of smoking on the process of developing CHD, including both short-term influences on platelets and other factors relating to thrombosis which may be more rapidly reversible and long-term increases in atherosclerosis which are only slowly reversible.

Persistent smokers may differ from those who quit in other ways that could affect the risk of developing CHD. A number of investigators have examined whether such differences would account for some or all of the decline in risk among those who stop smoking. The risk profiles of quitters and persistent smokers vary among studies: In some studies, there are no material differences; however, in other studies, quitters have a healthier profile; the opposite is true for still other studies. In the studies of primary prevention, none of these differences could explain even a minor portion of the decreased risk among quitters. Most studies of cessation after an MI have found that quitters had a higher baseline risk; however, their risk decreased compared with persistent smokers. Thus, both in primary and secondary prevention studies, confounding effects of other risk factors do not explain the apparent benefits of cessation. To the contrary, in many studies, the decrease in risk is even more pronounced after adjustment for baseline characteristics.

Only a few studies have examined the impact of smoking cessation in relation to various other CHD risk factors. No data are available to suggest that the relative risks differ substantially in the presence or absence of other CHD risk factors; that is, the percentage reduction in risk most likely occurs across risk factor categories. However, because individuals at high risk for other reasons such as family history, hypertension, or elevated cholesterol have higher rates of CHD, a given percentage decrease in risk among these individuals is a greater absolute decrease than among those with a lower risk profile. Hence, it is of especially great importance to achieve high rates of cessation among individuals who are otherwise at high risk for CHD.

Most data on the effects of smoking cessation are derived from white males, but sufficient information is available about women to indicate that the findings are similar for both sexes. Less is known about the effects of cessation among minority groups; however, there is no reason to believe that the benefits of cessation would be any different for these groups.

Several studies have examined the effect of smoking cessation after age 60 on subsequent CHD risk. Data are now available that demonstrate that the benefits of cessation extend to older adults as well as to young and middle-aged adults for both primary (Table 3) and secondary prevention (Hermanson et al. 1988). Although the relative risks of CHD among current smokers tend to be lower among older persons than among younger persons, smoking cessation among older persons can have a greater absolute effect because their rates of CHD are so much higher.

Considerable data address the effects of smoking cessation among individuals with diagnosed CHD. A reduction in risk of further CHD-related morbidity and mortality that accompanies smoking cessation has been conclusively demonstrated. Cigarette smoking is considered the leading modifiable CHD risk factor; overwhelming evidence demonstrates that cessation reduces that risk substantially.

SMOKING CESSATION AND AORTIC ANEURYSM

Abdominal aortic aneurysm refers to the dilatation or expansion of the aorta because of degenerative or inflammatory destruction of the components of the arterial wall. Most abdominal aortic aneurysms are a result of atherosclerosis, although other conditions cause abdominal aortic aneurysms. The preponderance of evidence from autopsy studies reviewed in the 1983 Report of the Surgeon General suggests that cigarette smoking aggravates or accelerates aortic atherosclerosis (US DHHS 1983). In addition, epidemiologic studies published up to that time indicated that smokers had elevated death rates from ruptured abdominal aneurysm compared with nonsmokers (Hammond and Garfinkel 1969; Hammond and Horn 1958a,b; Kahn 1966; Weir and Dunn 1970). Mechanisms whereby smoking causes atherosclerosis are reviewed in this Chapter.

Studies of Smoking Cessation and Risk of Aortic Aneurysm

Several of the larger prospective cohort studies reviewed above have reported results for mortality by cause of death. The data on mortality among former smokers from abdominal aortic aneurysms reported in five prospective cohort studies are summarized in Table 6. A consistent pattern is seen among men in these studies, with an excess risk of mortality approximately 50 percent lower among former smokers than among current smokers. However, excess risk among former smokers has remained about two to three times higher than that among never smokers. A similar pattern was also present for women in ACS CPS-II. Although data for women are limited, Doll and associates (1980) reported 11 deaths due to aortic aneurysm occurring during 22 years of followup among 6,194 women. Overall, these data indicate that former smokers have a reduced risk of death from aortic aneurysm compared with current smokers. More detailed analyses by duration of smoking abstinence have not been presented.

SMOKING CESSATION AND PERIPHERAL ARTERIAL OCCLUSIVE DISEASE

The peripheral arteries include those branches of the aorta that supply the upper and lower extremities and the abdominal viscera. Most peripheral arterial occlusive disease results from atherosclerosis, although other conditions may cause obstruction of these arteries. Symptomatic atherosclerosis of peripheral arteries occurs most often in the vessels of the lower extremities. The 1983 Report of the Surgeon General reviewed risk factors and epidemiologic data relating to the etiology of peripheral artery disease (US DHHS 1983). In that Report, an extremely strong association between cigarette smoking and diagnosis of peripheral artery disease was observed (US DHHS 1983). Cigarette smoking was the strongest risk factor for peripheral artery disease in the Framingham Study (Kannel, McGee, Gordon 1976). In this Section, the impact of smoking cessation on risk of developing peripheral artery disease is reviewed. In addition, the influence of cessation on treadmill time, rest pain, progression to amputation, and survival among patients with diagnosed peripheral artery disease is discussed.

TABLE 6.—Studies of smoking cessation and risk of death due to aortic aneurysm

Reference	Population	Follow up	Cases among former smokers		Standardized mortality ratios compared with never smokers	
					Former smokers	Current smokers
Doll and Peto (1976)	British physicians: 34,440 men	20 yr	30		3.2	5.2
Doll et al. (1980)	British physicians: 6,194 women	22 yr	NR		3.0	1–14 cig/day: 1.3 15–24 cig/day: 1.3
Rogot and Murray (1980)	US veterans: 293,958 men	15 yr	253		2.58	5.23
Carstensen, Pershagen, Eklund (1987)	25,129 Swedish men	16 yr	12		1.4	1–7 g/day: 1.7 8–15 g/day: 2.7 >15 g/day: 3.0
US DHHS (1989)	ACS CPS-I (25-State Study)	6 yr	NR	Women	3.67[a]	4.64
				Men	2.40	4.11

NOTE: NR=not reported; ACS CPS I=American Cancer Prevention Study I.
[a] Indicates current and former smokers.

Smoking Cessation and Development of Peripheral Artery Disease

Two studies provide sufficient detail to calculate the risk of peripheral vascular disease among former smokers compared with current smokers. Jacobsen and coworkers (1984) compared a consecutive series of 53 patients with intermittent claudication with age-matched controls free from symptoms of claudication. All patients with claudication were either current or former smokers. Among former smokers, the risk of developing peripheral arterial disease was 50 percent lower than that of current smokers.

Hughson, Mann, and Garrod (1978) reported risk factors for intermittent claudication among 54 patients and 108 controls. Smoking was the risk factor most strongly associated with the development of intermittent claudication. Former smokers had an estimated 58-percent lower risk than that of current smokers.

Smoking Cessation and Prognosis of Peripheral Artery Disease

In a study of 91 men with mild intermittent claudication monitored for at least 6 months, patients who stopped or decreased smoking had slightly less progression of symptoms during 2.5 years of followup, but this finding was not statistically significant (Cronenwett et al. 1984). Changes in treadmill exercise tolerance were assessed among 41 patients suffering from intermittent claudication who continued to smoke during the followup period and among 16 patients who stopped smoking after the first test and remained nonsmokers until the end of study (Quick and Cotton 1982). The maximum treadmill walking distance did not change significantly among continuing smokers (23 meter improvement, $p=0.17$). However, among those who stopped smoking, the improvement in maximum treadmill distance was statistically significant (86.2 meters, $p=0.02$). The two groups were not compared directly.

During a 6-year period, the risk of developing pain at rest was studied in 224 consecutive nondiabetic patients with intermittent claudication (Jonason and Ringqvist 1985). The cardiovascular risk profiles were almost identical for 30 never smokers and 34 patients who stopped smoking within 1 year after initial examination. These two groups were combined and compared with 160 patients who continued to smoke. The cumulative percentage of patients with pain at rest after 6 years was 8 percent among those who had stopped smoking within 1 year after the initial examination or who were never smokers; among smokers and those who stopped smoking more than 1 year after the initial examination, 21 percent developed pain at rest ($p<0.03$ after adjustments for difference in presence of multiple stenoses at baseline). These data are difficult to interpret because never and former smokers were combined, but suggest that the rate of development of rest pain is decreased among former and never smokers compared with those who continue to smoke.

In a followup study of 60 patients who underwent operation for intermittent claudication, those who stopped or reduced smoking after referral had a much improved prognosis (Hughson et al. 1978). At baseline, clinical characteristics or the number of cigarettes smoked did not differ between those patients who decreased or stopped smoking and those who continued to smoke during the followup period. The interval

between initial and repeat operations was significantly shorter in those who continued to smoke (Mann-Whitney test, $p<0.05$). Those who stopped or reduced smoking attained a significant improvement in overall survival by 12 months. A second series of 160 patients was studied for 8 years after their first hospital admission. Those who were smoking at the time of referral had a significantly poorer survival pattern than those who had stopped smoking or had reduced smoking. Similar results were observed by Jonason and Bergström (1987) who studied 343 consecutive patients with intermittent claudication and by Faulkner, House, and Castleden (1983) who studied 133 patients.

A retrospective record review was undertaken at Mayo Clinic to identify nondiabetic patients with a clinical diagnosis of arteriosclerosis obliterans, and Juergens, Barker, and Hines (1960) reported the survival and amputation rates among these patients. Of 159 patients who smoked at the time of diagnosis and who survived 5 years, 88 continued to smoke and 71 abstained from smoking after diagnosis. Of the total number of patients who continued to smoke, 11.4 percent required an amputation within the 5-year period. In contrast, none of the abstainers required amputation during this period.

In a recent retrospective 5-year followup study, Ameli and colleagues (1989) reported the rates of amputation and patency of 136 arterial reconstructions performed for lower limb ischemia. Of 121 patients, 103 smoked before the operation, and of the smokers 43 postoperatively discontinued smoking. The 34 patients who continued to smoke more than 15 cigarettes per day had a fivefold increase in risk for amputation at 2 years and a threefold increase in risk for amputation at 5 years compared with the 87 nonsmokers (including never and former smokers) and smokers of 15 cigarettes or less per day ($p=0.013$). Five years after surgery, 28 percent of patients smoking more than 15 cigarettes per day had undergone amputation compared with 11 percent of the patients who were nonsmokers or smoked 15 cigarettes or less per day.

The effect of smoking on the patency of femoropopliteal vein bypass grafts used for treating peripheral arterial occlusion was studied among 157 patients monitored for 1 year (Wiseman et al. 1989). Patients who continued to smoke, identified by elevated serum SCN^-, had a graft patency of 63 percent after 1 year compared with 84 percent among nonsmokers ($p<0.02$). However, the analysis did not separate never smokers from those who stopped smoking near or at the time of surgery ($p<0.02$). Only serum fibrinogen levels were a stronger predictor of graft failure than serum SCN^-.

Summary

Overall, these studies show a lower risk of peripheral artery disease among former smokers compared with current smokers and a consistent reduction in complications of peripheral vascular disease among patients who stop smoking. Those who quit have improved performance and improved overall survival.

SMOKING CESSATION AND CEREBROVASCULAR DISEASE

Stroke is the third leading cause of death in the United States. It is also a major cause of morbidity, with approximately 400,000 Americans suffering strokes each year (Graves 1989). The two major types of stroke are ischemic strokes due to occlusion of a vessel by an embolus or thrombus and hemorrhagic strokes resulting from subarachnoid or parenchymal hemorrhage. The terms cerebrovascular accident and stroke are nonspecific and usually refer to clinical syndromes resulting from cerebral infarction or hemorrhage. A thrombotic or embolic stroke may be caused by atherosclerotic disease of the extra- or intracranial blood vessels. Embolization from the heart or extracranial arteries is also an important cause of stroke. In the Framingham Study, atherothrombotic brain infarction (referred to in this Chapter as ischemic stroke) accounted for 52.9 percent of strokes (Wolf et al. 1988). Improved diagnostic methods have provided a better categorization of the causes of stroke.

The 1964 Report of the Surgeon General (US PHS 1964) noted a moderate increase in the mortality rate from cerebrovascular disease in cigarette smokers compared with nonsmokers in the original ACS 9-State Study (Hammond and Horn 1958a,b) and the U.S. Veterans Study (Dorn 1959). In the 1971 Report, six major prospective epidemiologic studies were reviewed (US DHEW 1971). Cigarette smokers in these studies experienced increased stroke mortality compared with nonsmokers. The 1980 Report noted that women who smoke have an increased risk of subarachnoid hemorrhage (US DHHS 1980). The 1983 Report reviewed the data associating cigarette smoking with stroke and found an increased risk of stroke among smokers that was most evident among younger age groups (US DHHS 1983). It also noted that female cigarette smokers have an increased risk of subarachnoid hemorrhage and that the concurrent use of cigarettes and oral contraceptives greatly increased this risk.

The 1989 Report of the Surgeon General reviewed four additional large cohort studies that addressed the relation between cigarette smoking and risk of stroke and concluded that cigarette smoking is a cause of stroke (US DHHS 1989).

In a recent meta-analysis, Shinton and Beevers (1989) summarized the relation between cigarette smoking and stroke using 32 separate case–control and cohort studies. The overall relative risk of stroke associated with cigarette smoking was 1.5 (95-percent CI, 1.4–1.6). Relatve risks differed considerably for the subsets of stroke: cerebral infarction 1.9, cerebral hemorrhage 0.7, and subarachnoid hemorrhage 2.9. Relative risks decreased with increasing age; for persons less than 55 years of age, the relative risk was 2.9; for those aged 55 to 74 years, the relative risk was 1.8; and for those 75 years and older, the relative risk was 1.1. A dose–response relation was observed between the number of cigarettes smoked and risk of stroke, and women had a slightly greater relative risk than men (RR=1.72 vs. 1.43).

Based on the data from ACS CPS-II, the 1989 Report of the Surgeon General estimated that 51 percent of cerebrovascular disease deaths among men aged less than 65 years were attributable to cigarette smoking, and among women of the same age, 55 percent of cerebrovascular disease deaths were attributable to smoking (US DHHS 1989). For persons 65 years of age or older, 24 percent of cerebrovascular disease

among men was attributable to smoking; among women, 6 percent was estimated to be attributable to smoking.

Studies of Smoking Cessation and Risk of Cerebrovascular Disease

In this Section, data from cross-sectional, case–control, prospective cohort, and intervention studies are reviewed. As discussed in Chapter 2, misclassification of former smokers because of recidivism during the followup period is a general concern in prospective studies. However, case–control studies of stroke are limited by the relatively high fatality rate for incident cerebrovascular events, particularly for subarachnoid hemorrhage. This often excludes many incident cases or forces the use of proxy information from next of kin or other relatives. In all epidemiologic studies of past smoking and risk of stroke, careful classification of stroke by pathophysiologic type is important. Details of the relation between past smoking and risk of stroke are presented in Tables 7 and 8 for each type of stroke reported by investigators.

Cross-Sectional Studies

In a cross-sectinal analysis of 1,692 black and white men and women admitted for diagnostic evaluation of the carotid arteries, Tell and coworkers (1989) reported a significant relation between cigarette smoking an the thickness of carotid artery plaque assessed using B-mode ultrasonography. Based on self-report, patients were characterized as either nonsmokers (never smoked or quit more than 10 years earlier), former smokers (quit between 10 years and 1 month earlier), or current smokers. After adjusting for a patient's age, race, sex, and history of diabetes mellitus and hypertension, the mean plaque scores differed significantly among the three smoking groups. The mean difference in plaque thickness compared with that which could be expected was –0.31 mm for nonsmokers, 0.04 mm for former smokers, and 0.32 mm for current smokers. The absolute difference in mean plaque scores between nonsmokers and current smokers was 0.63 mm (95-percent CI, 0.45–0.81 mm), between nonsmokers and former smokers, 0.35 mm (95-percent CI, 0.17–0.54 mm), and between former and current smokers, 0.27 mm (95-percent CI, 0.08–0.47 mm). These data suggest a slower rate of progression of atherosclerosis among persons who have quit smoking compared with those who continue to smoke.

In a cross-sectional study of cerebral blood flow levels in 268 neurologically normal volunteers, Rogers and coworkers (1985) observed that subjects who quit smoking had significantly higher cerebral perfusion levels than subjects who continued to smoke.

Case–Control Studies

Case–control studies addressing the relation between smoking and risk of stroke are summarized in Table 7. In many other published case–control studies, former smokers have not been specifically identified as a distinct exposure group. In those studies that identify former smokers, the number of cases has been very small or unspecified except for the study by Donnan and colleagues (1989). In several studies (Bell and Ambrose

TABLE 7.—Case–control studies of smoking cessation and risk of stroke

Reference	Source and case–control numbers	Outcome	Strokes among former smokers		Relative risk as compared with never smokers[a] Former smokers	Current smokers
Bonita et al. (1986)	New Zealand: 132 cases; 1,586 community controls	Stroke, excluding subarachnoid hemorrhage	NR		1.4 (0.8–2.6)	2.4
Bonita (1986)	New Zealand: 115 cases; 1,586 community controls	Subarachnoid hemorrhage	NR		1.0 (0.5–1.9)	3.8
Bell and Ambrose (1982)	Scotland: 236 cases; general population control; (sample from survey by Tobacco Research Council)	73.3% of consecutive series with smoking data recorded		Men		
			10	Hemorrhage	0.19	0.16
			4	Infarction	0.14	0.88
			1	Hemorrhagic infarction	0.63	1.14
				Women		
			3	Hemorrhage	0.58	0.76
			1	Infarction	0.33	1.99
			0	Hemorrhagic infarction	NR	3.00
Taha, Ball, Illingworth (1982)	England: 178 cases, compared to UK population	Survived subarachnoid hemorrhage	7	Men	2.1[b]	4.7
			12	Women	1.5	2.6

TABLE 7.—Continued

Reference	Source and case/control numbers	Outcome	Strokes among former smokers	Relative risk as compared with never smokers[a]		
					Former smokers	Current smokers
Bell and Symon (1979)	England: 106 men, 1,628 women; general UK population 1965	Subarachnoid hemorrhage	NR	Men Women	1.92 2.52	3.89 3.72
Collaborative Group for the Study of Stroke in Young Women (1975)	US: 430 cases (15–44 yr); 429 hospital controls; 451 neighborhood controls	Thrombosis Hemorrhage	21 26		1.14 1.76	1.18 3.27
Donnan et al. (1989)	422 consecutive cases; 422 community controls	Cerebral ischemia	145		2.0 (1.3–3.1)	3.7
				Quit <2 yr	3.2	
				2–5 yr	3.1	
				5–10 yr	2.1	
				>10 yr	1.7	

NOTE: NR=not reported.
[a]95% confidence interval shown in parentheses when available.
[b]Relative risk calculated from data presented in original paper.

1982; Taha, Ball, Illingworth 1982; Bell and Symon 1979), population smoking rates rather than a true concurrent control group were used for comparison purposes. Despite these limitations, the risk of stroke among former smokers has been consistently lower than that among current smokers. Data for subarachnoid hemorrhage (Bell and Symon 1979; Taha, Ball, Illingworth 1982) show a persistent elevation in risk among former smokers compared with never smokers; however, this risk is lower than among current smokers.

Prospective Cohort Studies

To date, a total of 14 prospective cohort studies have reported sufficient detail to categorize former smokers as a specific subgroup monitored for incidence of stroke. These studies have obtained information on smoking status at baseline through interview or self-administered questionnaire and have observed populations for 2 years (Nomura et al. 1974) to 26 years (Wolf et al. 1988). Other cohort studies have reported the relation between cigarette smoking and stroke but have not included sufficient details to categorize ex-smokers as a unique exposure group.

In each of the studies included in Table 7, the risks among former smokers and among current smokers are reported compared with the risk among never smokers. The earlier prospective studies tended not to show a positive relation between smoking and stroke, and in several studies, the risk among past smokers was higher than that among current smokers. In a multivariate analysis of data from the Whitehall Civil Servants Study (18,403 male British civil servants), the relative risk of stroke was 2.2 among current smokers of 15 cigarettes per day compared with never smokers, whereas the relative risk among former smokers was 1.5 (Fuller et al. 1983). Among British women, current smokers experienced a 3.0 relative risk of subarachnoid hemorrhage, and former smokers experienced a 2.3 relative risk (Vessey, Lawless, Yeates 1984). Lower elevations in risk were found among individuals experiencing ischemic strokes.

No excess risk of stroke was observed among 2,748 current or former smokers, residents of Cook County, IL (Ostfeld et al. 1974), or in 47,423 residents of Washington County, MD (Nomura et al. 1974). Doll and Peto (1976) studied 34,440 male British physicians for 20 years and updated information on cigarette smoking after 6 and 15 years. These researchers used similar methods for studying female British physicians among whom smoking status was updated after 10 years (Doll et al. 1980). Only slight elevations in risks of stroke were seen among male current or former smokers, and no excess risk was found among female current smokers. Similarly, Okada and colleagues (1976) found no significant elevation in risk of stroke among current or former smokers in a Japanese population.

In 14 cohort studies published after 1980, the relative risks among former smokers were lower than those reported for current smokers (Table 7). Rogot and Murray (1980) observed U.S. veterans and defined the population of former smokers as those who had stopped smoking for reasons other than a doctor's orders. These former smokers had a relative risk of 1.02; current smokers had a relative risk of 1.32.

In a study of 7,895 Hawaiian men of Japanese ancestry (Abbott et al. 1986), 658 smokers who quit in the first 6 years of followup were monitored for another 6 years;

their age-adjusted relative risk for total stroke was 1.5 compared with never smokers (95-percent CI, 1.0–2.3). Risks were similar for ischemic and hemorrhagic strokes. Concurrently, current smokers had a relative risk of 3.5 compared with never smokers. Former smokers had a significant reduction in risk of total stroke compared with current smokers ($p<0.05$). This analysis suggests that after adjusting for other risk factors, former smokers may be at increased risk of stroke. This residual risk may be due to the irreversibility or slow reversibility of the underlying mechanisms of smoking-attributable stroke, or the resumption of smoking among former smokers.

Welin and colleagues (1987) followed 789 men born in 1913 for 18.5 years. Smoking information was updated during a followup examination after 6 years. Investigators then identified a subgroup of former smokers who were monitored for 12 years. Among these former smokers, the relative risk of stroke was 1.18 compared with 1.67 for current smokers.

Wolf and coworkers (1988) studied 4,255 men and women in the Framingham Study and updated cigarette smoking information at 2-year intervals. Among current smokers, the relative risks of overall stroke were 1.42 for men and 1.61 for women. During the 26 years of followup, 50 percent of the normotensive smokers quit smoking compared with 44 percent of the hypertensive smokers ($p<0.05$). Former smokers had a significantly lower risk compared with current smokers. This relation was observed among men and women in each of the blood pressure categories. Benefits of smoking cessation were observed in the hypertensive and normotensive subjects.

In the Nurses Health Study, current smoking was strongly associated with risk of both subarachnoid hemorrhage and thromboembolic stroke (RR=10.3 and 3.1, respectively, for 25 cigarettes or more per day) (Colditz et al. 1988). The relative risks for former smokers were substantially lower.

As described in the 1989 Report of the Surgeon General, the relative risks of stroke for smokers showed an increase when CPS-II data from 1982 to 1986 were compared with CPS-I data from 1959 to 1965 (US DHHS 1989). These studies, using the same design and methods, showed an increase in the relative risk of death from stroke among current smokers for men aged 35 to 64 years from 1.79 in 1959–65 to 3.67 in 1982–86. For women of the same age, the relative risk increased from 1.92 to 4.80. The number of former smokers among women in CPS-I was too small to report these data separately. However, for males, the relative risk of stroke among former smokers has shown little increase and remained only slightly higher than among never smokers.

The reasons are unclear for the stronger associations between cigarette smoking and risk of stroke noted in more recent studies. However, this tendency for higher relative risks in the more recent studies has been documented for a wide variety of smoking-related diseases (US DHHS 1989). One likely explanation is that the effect of smoking is related to duration of smoking, and the cohorts of persons (especially women) who started smoking before age 20 are only now reaching middle and late adulthood (Garfinkel and Stellman 1988). Control of hypertension has improved in the United States during the last decade, and the incidence of stroke has declined. Thus, smoking may now play a relatively greater role in the etiology of this disease than it did in earlier periods when uncontrolled hypertension was more common.