Risk of CHD in Women

Young and middle-aged women experience only one-fifth the incidence and mortality from CHD of men (*16, 40, 94, 101, 139, 244, 255, 283*). These rates are steeply age dependent, and rates in young and middle-aged women lag behind those in men by about 10 years. Reasons for the sex-dependent differences are incompletely understood, but this protective influence of female sex is partly due to differences in cigarette smoking and other behavioral variables (*6, 58, 103, 127, 128, 150, 151, 166, 170, 203, 204, 210, 227, 234, 243, 244, 255, 267, 270, 280*).

During the 1950s and 1960s, when the previously reported large-scale investigations of smoking and CHD were conducted, relatively few women smoked, and on the average, those who did began at an older age, smoked fewer cigarettes, and inhaled less than men (*261*). During the past two decades, women have begun to smoke cigarettes at younger ages, and their cigarette smoking habits have become more like those of men (*261*). Observations by a number of investigators have shown that the incidence of CHD in recent years in women who smoke cigarettes is far greater than the very low rates that are observed in women who do not smoke, and the incidence of CHD in women who smoke heavily may be similar to the incidence in men.

To observe the effect of cigarette smoking in women more specifically, studies have been performed to take account of potentially confounding influences on the occurrence of CHD. Slone et al. (*244*) in Boston observed cases and matched controls from a large number of U.S. hospitals between July 1976 and December 1977. During this 18-month period, 55 cases of nonfatal MI were identified in women under age 50 who had not used oral contraceptives within the month prior to admission and who had not been under treatment for heart disease or related disorders. The estimated relative risk for smokers compared with nonsmokers was 6.8 ($p < 0.001$). In light smokers (1 to 14 cigarettes per day) the relative risk was 4.4, and in heavy smokers (more than 35 cigarettes per day) the relative risk was 21. The relative risk appeared as great in those who had not experienced menopause as in those who had experienced menopause. In those young women with no known risk factors other than cigarette smoking, the data indicated that the smoking habit accounted for 76 percent of the risk of nonfatal MI (*244*). This magnitude of relative and attributable risk with smoking in otherwise healthy young women is consistent with similar observations in young men.

A subsequent report included cases observed through August 1978 with and without the following characteristics: obesity, diabetes mellitus, abnormal blood lipids, hypertension, angina pectoris, history of preeclampsia, coffee consumption, and oral contraceptive

(OC) use (*227*). Smoking was confirmed as a singularly strong risk factor (Figure 10). Relative risk increased exponentially with the number of cigarettes smoked, and the relative risk in younger women was greater than in older women. A gradient of risk with increasing level of cigarette smoking was also observed in subjects who had one or more of the other risk factors. In those at the highest level of risk, women smoking 35 or more cigarettes per day who had one or more predisposing risk factors, the relative risk was 31.

A number of investigations have been performed to observe the effects of OC use, and there is substantial evidence for interaction of the smoking effect with OC use as well as other risk factors. These data suggest that the biological effect of multiple risk factors, particularly when combined with OC use, may be multiplicative for the risk of CHD. Shapiro et al. (*242*) found that women who smoked more than 25 cigarettes per day but did not use OCs experienced a relative risk of MI of 7 in comparison with nonsmoking women who did not use OCs. Nonsmokers who used OCs experienced a relative risk of MI of 4.5. The women who combined both behaviors had a relative risk of MI of 39. In a case–control study of factors related to MI in nurses in the United States, Rosenberg et al. (*226*) reported relative risks with OC use, smoking, and hypertension of 3, 5, and 8, respectively; however, in nurses with all three characteristics the relative risk was 170.

Comparable results were observed in England by Mann, where the relative risk for MI in women with major cardiovascular risk factors (including cigarette smoking) who used OCs was up to 128 times that of women free of these characteristics (*169*). The importance of cigarette smoking to the incidence of MI in women has been confirmed by other studies in England (*211, 270*), Sweden (*16, 279*), Scotland (*203*), Finland (*234*), and elsewhere.

In addition to the excess risk of nonfatal MI and death from CHD, sudden cardiac death in women has been observed to be strongly related to the cigarette smoking habit (*249, 254*). However, the relationship of angina pectoris to cigarette smoking is uncertain. As in men, some studies have shown a positive relationship with smoking (*271*), but other studies have found no significant difference in the occurrence of angina pectoris between female smokers and nonsmokers (*16, 40, 203*).

CHD incidence and mortality in women increase remarkably after the menopause. Before the menopause, cases of CHD may be limited largely to women who smoke (*15, 16, 138*). Furthermore, there is evidence that the menopause occurs at an earlier age in women who smoke than in women who do not smoke (*129, 270*). Willet et al. (*282*) observed a progressive increase in the risk of early menopause with an increasing level of daily use of cigarettes, and cigarette smoking was more closely related to early menopause than any other factor

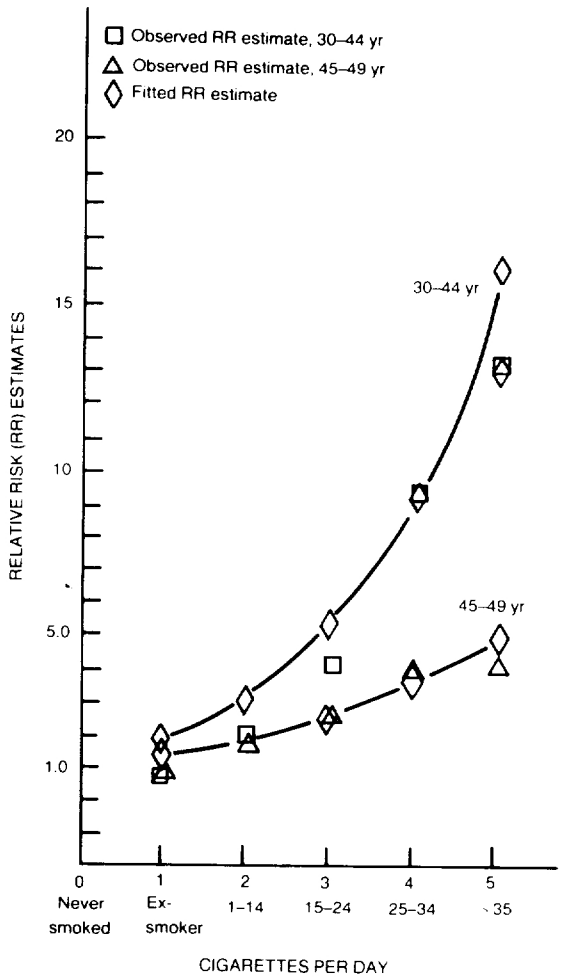

FIGURE 10.—Relation to relative risk of myocardial infarction to cigarette smoking, according to age

NOTE: Difference in slopes: $\chi_1^2 = 2.7$, $p_2 = 0.10$.
SOURCE: Rosenberg et al. (*227*).

considered. The evidence that a combination of cigarette smoking with the use of oral contraceptives potentiates (multiplies) the occurrence of CHD is strong, but the mechanisms are not adequately understood. The use of noncontraceptive estrogens was not associated with an excess risk of MI (*228*). Furthermore, menopausal estrogen therapy has been associated with a protective effect from CHD death (*231*). There is evidence that both cigarette smoking and

progestins in oral contraceptives depress high density lipoprotein cholesterol (HDL-C), and HDL-C appears to protect from CHD (*13, 23, 35, 41, 59, 62, 74, 78, 122, 123, 213, 215, 265, 266, 269, 281*). Those with low levels of HDL-C have been shown to suffer higher rates of CHD than those with high levels of HDL-C (see Interaction of Cigarette Smoking and Other Risk Factors above).

Whatever the mechanism, it must be concluded that women who decide to smoke assume a substantially increased risk of CHD, and that the risk for women who smoke heavily approaches the risk of CHD for men. The relative risk of cigarette smoking is greater in younger women than in older women, and the relative risk increases progressively with the number of cigarettes smoked. Women who smoke have been observed to experience menopause earlier than women who do not smoke, and this may also increase the CHD risk for women who smoke. A synergistic interaction between cigarette smoking and other risk factors for CHD has been demonstrated for women, particularly for oral contraceptive use. More investigation is required to evaluate this phenomenon; an astonishingly high relative risk of CHD occurs in women who smoke cigarettes and also have other risk factors, including use of oral contraceptives.

Risk of Sudden Cardiac Death

The definition of sudden cardiac death (SCD) is discussed in the introduction to this section. In a number of studies, severe CHD has been observed in a large proportion of the cases that have succumbed to SCD (*10, 12, 139, 153, 154, 156, 157, 160, 162, 200, 208, 248*).

In several epidemiologic studies, cigarette smoking has been even more closely related to SCD than to CHD in general. After 24 years of followup in the Framingham study (*40, 139*), the risk of SCD in cigarette smokers was found to be three times that in nonsmokers, and a comparable relative risk was observed in the five-cohort Pooling Project data (*124, 251*). Although the relative risk in young men was greater than in older men, the relative risk was 2 even in men aged 70 to 79 in the Framingham cohort (*40*). In the Pooling Project data, the 10-year incidence of SCD increased progressively with the number of cigarettes smoked per day, analogous to the relationships with the first major coronary event or with all CHD deaths (*124, 251*). Other studies confirming the importance of cigarette smoking in SCD include members of the Kaiser-Permanente health plan in the San Francisco Bay area (*68*), black and white men and women in Baltimore (*156*), men employed in the telephone industry throughout the United States (*110*), and men living in Scandinavia (*72, 220*).

Other risk factors used to predict the occurrence of SCD include hypertension, high relative weight, high serum cholesterol, left ventricular hypertrophy by electrocardiogram, and alcoholism (*50,*

64, 68, 109, 137, 139, 149, 152, 153, 156, 173, 188, 209, 216). In multivariate analysis of the combined Framingham and Albany data for men aged 45 to 64, cigarette smoking emerged with the highest level of statistical significance among five risk factors predicting SCD (*137*).

Approximately half of those who experience SCD have preexisting clinical evidence of CHD (*109, 139, 153, 154, 220*). In a study by the Health Insurance Plan of Greater New York it was found that in comparison with patients who stopped smoking, those who continued to smoke after myocardial infarction or after the onset of angina pectoris experienced twice the risk of death over the subsequent 4 1/2-year period of followup (*242*). Results supporting this observation have been observed in some other studies (*69, 141, 155, 233, 238, 250*).

The results of numerous studies have consistently identified cigarette smoking as a leading factor in SCD. This is true for men and women, and the risk increases with the number of cigarettes smoked per day.

Prospective Mortality Studies

The detailed epidemiologic studies of CHD incidence described elsewhere in this section establish the close association between cigarette smoking and the subsequent development of coronary heart disease. The possibility that this association can be confounded by other characteristics with which smoking is associated has been intensively examined in these studies. The relationship between cigarette smoking and CHD has been demonstrated to exist independent of the presence of other risk factors.

Studies using CHD mortality as an end point can be performed at a lower cost than can studies of the incidence of the disease. This allows the inclusion of larger numbers of individuals in order to examine the effects of smoking in larger segments of the population. It also provides sufficient numbers of cases for detailed analyses of the effects of dose, age, smoking cessation, and other variables of interest. Studies examining the relationship between cigarette smoking and subsequent CHD mortality are now available for a variety of populations and include over 20 million person-years of observation. In the 10 largest studies the results are remarkably similar. Whether in the United States, Canada, the United Kingdom, Scandinavia, or Japan, smokers as a group experience excess CHD mortality that is approximately 70 percent above that of the nonsmokers.

In the following paragraphs, the major studies that have prospectively examined the relationship between cigarette smoking and CHD mortality are discussed. The number of individuals followed in these studies allows a detailed examination of the nature of this

relationship, including the changes in risk that occur with age, the relationship between dose of cigarette exposure and CHD risk, the effects of low tar and nicotine cigarettes, the risk of pipe and cigarette smoking, and the benefits of cessation.

Overall CHD Risk for Men and Women

A number of major prospective studies have examined the relationship between cigarette smoking and CHD mortality in men and women. Under this heading, a description of the populations studied and the findings for overall CHD risk in those populations are presented. Under subsequent headings, the questions of the differences in risk that occur with age, increasing dosage of cigarette exposure, low tar and nicotine cigarettes, pipe and cigar smoking, and the effects of cessation are examined on the basis of the evidence from these prospective studies.

In the United States, Dorn initiated a study of U.S. veterans who had served in the Armed Forces between 1917 and 1940 and who had U.S. Government life insurance policies in force in December 1953. This initial cohort of 293,658 persons was mailed a questionnaire in 1954, and the nonrespondents were followed up again in 1957. Responses were obtained from 248,046 veterans, with an overall response rate of 85 percent. Reports for 2 1/2 years (*46*) and 8 1/2 years (*131*) of followup were reviewed in detail in prior reports of the Surgeon General. The 16-year followup has been completed by Rogot and Murray (*224*). Death certificates were located for 85,323 (98 percent) of those original questionnaire respondents who died. Confirmation of the cause of death shown on the death certificate was investigated by Dorn (*46*). Whenever a death occurred in the United States, clinical confirmation concerning cause of death was sought from the physician who signed the death certificate. A response was obtained in 99 percent, and after review of the cause of death based on clinical data, only 6 percent of the deaths were reassigned to a cause different from that originally indicated on the death certificate. This degree of confirmation is considered good. Coronary heart disease mortality was 58 percent higher in cigarette smokers than in nonsmokers (Table 8), and CHD accounted for more excess deaths than any other cause of death.

In 1952, the 9-State study by the American Cancer Society was initiated; 187,783 white males, aged 50 to 70, were followed for an average of 44 months. There were 11,870 deaths. Of these deaths, 5,297 were due to coronary heart disease (*96*). A highly significant excess mortality was observed in smokers as compared with nonsmokers. The death rate for coronary heart disease was 70 percent higher in smokers compared with nonsmokers (Table 8).

In late 1959 and early 1960, the American Cancer Society enrolled 1,078,894 men and women from 25 States in a prospective study that

TABLE 8.—Coronary heart disease mortality ratios, major prospective studies

Population/ Study	Size	No. of CHD deaths	Mortality ratio		Comments
			Nonsmoker	Cigarette smoker	
U.S. veterans	290,000 males	34,874	1.00	1.58	
ACS 9-State study	188,000 males	5,297	1.00	1.70	
Japanese in 29 health districts	122,000 males 143,000 females	3,351 2,653	1.00 1.00	1.71 1.78	
ACS 25-State study	358,000 males 483,000 females	10,771 4,048	1.00 1.00	1.90–2.55 *	Male data for two levels of smoking intensity, see Table 12; *female data available by age and amount smoked only, see Tables 9 and 14
Canadian veterans	78,000 males	3,405	1.00	1.60	
British physicians	34,000 males 6,195 females	3,191 179	1.00 1.00	1.62 *	*Female data available by amount smoked only, see Tables 9 and 12
Swedish study	27,000 males 28,000 females	916 457	1.00 1.00	1.70 1.30	
California males in 9 occupations	68,000 males	1,718	1.00	1.60	
Swiss physicians	3,749 males	280	1.00	1.33–2.18	Data available by amount smoked only, see Table 12

was the largest of its kind ever conducted. All segments of the population were included, with the exception of groups that could not be easily traced. An initial demographic questionnaire recorded height, weight, detailed information concerning smoking (types of tobacco used, number of cigarettes smoked per day, inhalation, age at which smoking began, brand of cigarettes used), and other variables that might influence mortality. Hammond reported cause-specific mortality for the initial followup through September 1963 (97.4 percent successfully traced) on all those aged 35 to 84 at the time of enrollment (*93*). In men, 1,639,211 person-years of experience were observed, and in women, 2,125,360 person-years of experience were observed. Death certificates were obtained in 97.9 percent of the 25,895 deaths. CHD mortality ratios in male cigarette smokers

compared with those who never smoked regularly varied from 2.81 in men aged 45 to 54 to 1.24 in men aged 75 to 84 (Table 9). Ratios for women were 2.00 and 1.19 for age 45 to 54 and 75 to 84, respectively. In the 6-year followup reported by Hammond and Garfinkel (*94*), there was a total of 28,446 deaths. Using the death rates of nonsmokers as the standard, over 11,500 excess deaths were attributable to smoking. Coronary heart disease accounted for 46 percent of the excess deaths in men and 40.6 percent of the excess deaths in women.

A study of California men in various occupations was begun in 1954, and 68,153 men aged 35 to 64 were followed for mortality through December 1962 (*234*). Smokers included current as well as ex-smokers. Nonsmokers were all men who had never regularly smoked cigarettes for even 1 year, and pipe and cigar smokers were included in this group. A total of 4,706 men were identified. The mortality ratio for CHD was 1.6 (60 percent excess CHD mortality) in smokers as compared with nonsmokers.

San Francisco longshoremen were studied by Paffenbarger et al. (*205*); 3,686 men aged 35 to 74 were examined in 1951 and followed for 22 years. A total of 1,270 deaths were observed during 55,635 person-years of observation. After adjusting for difference in age, systolic blood pressure, and level of activity, the CHD mortality ratio for those smoking 20 cigarettes or more per day was 2.09 relative to those subjects who smoked fewer cigarettes or none.

Gillum and Paffenbarger reported CHD mortality from followup of 13,728 university students examined between 1939 and 1950 (*77*). CHD morbidity followup was observed in 8,852 who had returned self-administered questionnaires in 1962, 1966, or 1972. Four control subjects were randomly assigned to each of the 98 cases of fatal CHD, 78 cases of myocardial infarction, and 49 cases of angina pectoris. Fatal CHD, MI, and angina pectoris were strongly associated with smoking history; relative risks were near 2.5. Association with fatal CHD, or with MI, or both, was also apparent for a family history of CHD, weight, height, and systolic blood pressure.

The Canadian Department of National Health and Welfare initiated a study in 1955 of smoking and health in disability pensioners, principally veterans of World Wars I and II. Best reported the results of a 6-year followup in 1966 (*17*). The 78,000 Canadian men were aged 30 to 90 at the onset of the study. Smoking habits were determined at the start of the study. Nonsmokers were respondents who had never smoked. Ever smokers were those who had smoked at least 100 cigarettes during their lifetime or 10 cigars or 20 pipefuls of tobacco. Current smokers were those who reported smoking at the start of the study. Ex-smokers were those who had smoked previously, but had stopped smoking at the start of the study. During the 6-year followup, 9,491 deaths were observed, of

TABLE 9.—Coronary heart disease mortality ratios and rates, by age and smoking habit, prospective studies

Study	Mortality ratio and (rate)[1] by age				
ACS 25-State	35–44	45–54	55–64	65–74	75–84
Male nonsmoker	1.00(—)[2]	1.00(150)	1.00(542)	1.00(1400)	1.00(3132)
Male smoker	— (148)	2.81(422)	1.84(996)	1.45(2025)	1.24(3871)
Female nonsmoker	1.00	1.00(33)	1.00(163)	1.00(653)	1.00(1973)
Female smoker	—	2.00(66)	1.69(275)	1.44(941)	1.19(2349)
U.S. veterans	35–44	45–54	55–64	65–74	75–84
Nonsmoker or occasional only	1.00(18)	1.00(50)	1.00(501)	1.00(1015)	1.00(2216)
Cigarettes only	4.44(80)	7.00(353)	1.80(880)	1.60(1659)	1.20(2683)
Japanese in 29 health districts	40–49	50–59	60–69	70+	
Male nonsmoker	1.00(8.0)	1.00(48.3)	1.00(105.5)	1.00(189.6)	
Male smoker	3.09(24.7)	1.42(68.8)	1.62(170.7)	1.71(323.8)	
Female nonsmoker	1.00(6.1)	1.00(23.6)	1.00(79.5)	1.00(109.4)	
Female smoker	1.46(8.9)	1.75(41.2)	1.54(122.5)	1.44(157.9)	
ACS 9-State	50–54	55–59	60–64	65–69	
Nonsmoker	1.00(271)	1.00(431)	1.00(733)	1.00(1247)	
Smoker	1.92(521)	1.85(801)	1.66(1219)	1.41(1759)	
British physicians, male		<65		≥65	
Nonsmoker		1.00(189)		1.00(1655)	
Current, cigarettes only		2.19(413)		1.37(2259)	
British physicians, female					
Nonsmoker		1.00(31)		1.00(511)	
Smoker 1–14 cigarettes		1.41(44)		0.78(402)	
15–24 cigs		2.54(79)		2.18(1117)	
25+ cigarettes		2.74(85)		2.76(1411)	
Canadian veterans	55–59	60–64	65–69	70–74	75–79
Nonsmoker	1.00	1.00	1.00	1.00	1.00
Cigarettes only	1.90	1.61	1.38	1.79	1.45
Swedish prospective	18–39	40–49	50–59	60–69	
Nonsmoker	1.00	1.00	1.00	1.00	
Male smoker, cigs only	—	2.60	1.70	1.70	
Female smoker	—	—	2.60	1.10	
Swiss physicians	35–54	55–65	66–74	75+	
Nonsmoker	1.00	1.00	1.00	1.00	
Heavy smoker[3]	2.30	2.20	1.90	1.00	
California males in 9 occupations	35–44	45–54	55–64	65–69	
Nonsmoker	1.00	1.00	1.00	1.00	
Smoker	6.24	2.95	1.56	1.24	

[1] Rate per 100,000, unless otherwise stated.
[2] Number of deaths too small to compute a ratio.
[3] Heavy smoker: one or more packs per day.

which approximately 2,000 were attributed to coronary heart disease. Smokers experienced a death rate 68 percent higher than

that of nonsmokers. The excess mortality was due mainly to cardiovascular disease, with coronary heart disease alone accounting for 36 percent of the excess. The death rate due to coronary heart disease in smokers was 60 percent higher than the death rate in nonsmokers (Table 8).

In 1951, a study of mortality in British physicians was initiated. The results were reported by Doll and Hill (*44*) and subsequently by Doll and Peto (*45*) and by Doll et al. (*43*). A total of 34,400 men responded to the questionnaire (69 percent response rate). Followup questionnaires were sent in 1957, 1966, and 1972. Twenty-year mortality through October 1971 was reported in 1976 (*45*). Virtually all of the sample had been traced, and 10,072 deaths were identified. Nonsmokers were defined as those who had never smoked as much as one cigarette per day for as long as 1 year. Smoking status was updated using the information from followup questionnaires. Coronary heart disease accounted for 3,191 of the deaths. Information from the first questionnaire was related to the deaths occurring in the first 7 years, information from the second questionnaire to deaths in the next 8 years, and information from the third questionnaire was related to deaths in the last 5 years of the followup period. The death rate for smokers of all forms of tobacco was 37 percent higher than the death rate for nonsmokers.

Results of the 22-year mortality followup of female British physicians were reported recently (*43*). Among 6,194 respondents there were 1,094 deaths. Coronary heart disease was the underlying cause of death in 179. Among smokers, excess mortality was observed only for those smoking 15 or more cigarettes per day, but for these women the relative risks exceeded 2. The coronary heart disease mortality of all female smokers was only 35 percent of that of all male smokers. Those women who smoked more heavily (15 or more cigarettes per day) experienced CHD mortality that was 67 percent of that of men who smoked more than 15 cigarettes per day. Further analyses indicated that these female smokers had a lower cumulative smoking exposure than the male smokers; the female smokers had begun smoking at later ages and smoked fewer cigarettes, and fewer reported inhaling cigarette smoke. The CHD deaths among the female smokers were too few for more detailed analysis of the risk at levels of smoking behavior comparable to the most intense male smokers.

Examinations were given and questionnaires administered to 18,403 British civil servants working in London (*105*). Blood pressure, plasma cholesterol, blood glucose, height, weight, and relevant data were collected in a standardized fashion. During the 10-year followup there were 1,657 deaths, of which 704 were due to coronary heart disease. Grade of employment was significantly related to death from coronary heart disease; those at the highest grades

(administrators and professionals) experienced the lowest rates. However, at each grade of employment cigarette smokers experienced higher mortality than nonsmokers. The mortality of ex-smokers was similar to that of nonsmokers.

Grundy (*89*) reported the relationships of smoking habit and worksite exposure to carbon monoxide for 4,924 steelworkers in Ebbwvael, Wales, who were examined in 1964. After 10 years, 99 percent of the population surveyed was traced and 740 deaths were recorded. The total mortality and CHD mortality were higher than average for England and Wales. The smokers (73 percent of the sample) experienced a coronary heart disease mortality that was 80 percent higher (relative risk 1.8) than that of nonsmokers. Occupational exposure to carbon monoxide appeared to play a negligible role, in comparison with the importance of cigarette smoking, for coronary heart disease mortality. The high smoking rate in this population explained a substantial part of the excess mortality of this population compared with the average mortality for England and Wales.

In 1963, a probability sample of Swedish men and women aged 18 to 69 was surveyed by Cederlof et al. (*31*), and mortality was observed during the subsequent 10 years through December 1972. There were 25,444 male respondents (93 percent) and 27,342 female respondents (95 percent). In 1969, a followup questionnaire of a subsample indicated that smoking habits had not changed substantially since 1963 in the majority of those surveyed; for example, 78 percent of men and 63 percent of women who reported smoking 16 or more cigarettes per day in 1963 reported the same cigarette habit in 1969. During the 10-year followup, a total of 5,655 deaths were ascertained. Overall coronary heart disease mortality was 70 percent higher in male cigarette smokers and 30 percent higher in female cigarette smokers than in nonsmokers (Table 8). The possibility of confounding by other factors was evaluated. For univariate analysis, lower income and listing with the Swedish Alcohol Registry were associated with significantly higher CHD mortality. (In Sweden, violators of laws related to the use of alcohol, e.g., public drunkenness, drunk driving, illegal alcohol sales, are required to be registered.) However, cigarette smokers in each of these groups had significantly higher CHD mortality than never smokers, and the differences were particularly marked at higher levels of cigarette consumption. The CHD relative risks were also significantly higher for cigarette smokers within the high income group, among rural residents, and among those not listed in the Alcohol Registry.

In the Stockholm prospective study, risk factors for ischemic heart disease were evaluated in 3,486 men and 2,738 women who were first examined in 1961 through 1962 (*22*). During a 14 1/2-year followup, a total of 694 deaths were observed, of which 48 percent in men and

31 percent in women were attributed to ischemic heart disease. Of 235 ischemic vascular deaths in men, 189 were attributed to myocardial infarction. In univariate and multivariate analyses, cigarette smoking was significantly and independently related to the risk of ischemic vascular death in both sexes.

In 1955, a survey on the smoking habits of 3,749 Swiss physicians was initiated. The first reported findings (*252*) after 9 years of observation were similar to the findings in the British physicians study of Doll and Hill (*44*). More recently published data, based on 18 years of followup (*90*), recorded 1,212 deaths among those physicians who completed questionnaires during the original survey and for whom complete information concerning cause of death was available. A total of 280 coronary heart disease deaths (59 nonsmokers and 221 smokers) were reported. CHD mortality ratios increased with increasing number of cigarettes per day. Light smokers (10 or fewer cigarettes per day) had a mortality ratio of 1.33, increasing to 2.18 with the heaviest amount smoked (35 or more cigarettes per day). Mortality for CHD among smokers tended to be greater in the younger age groups than in the older age groups.

Hirayama has reported followup at 8, 10, and 13 years for 122,261 men and 142,857 women over 40 years of age who were residents in 29 health districts in Japan (*111–116*). There was an overall 95 percent participation rate, and ascertainment of cause of death was virtually 100 percent. In the 13-year followup, over 3 million person-years of risk and 39,127 deaths (22,946 in men and 16,181 in women) were observed. Heart disease was certified in 3,351 men and 2,651 women. At the time of the baseline survey, the proportion of smokers was 76 percent in men and 10.5 percent in women. Mortality ratios for smokers were 1.7 for men and 1.8 for women. The possibility of confounding by other factors was evaluated through cross-classification of smoking by social class, consumption of meat and milk, and alcohol consumption. Higher coronary heart disease mortality was observed with higher social class and among those consuming more meat and milk. Alcohol intake was inversely related to coronary heart disease mortality. At both high and low levels of these characteristics, however, the risk of death from CHD among smokers remained higher than among nonsmokers. The proportion of coronary heart disease mortality attributed to cigarette smoking in this population was 34.3 percent for men and 9.5 percent for women.

CHD mortality, as well as CHD incidence, is clearly much higher in cigarette smokers than in nonsmokers. This excess mortality occurred uniformly in each of the major prospective studies. It also occurred in populations of markedly different ethnic background and geographical location. The relationship also persisted when a number of other confounding variables were taken into account. The risk was somewhat lower for women, but in those groups of women

whose smoking habits approximated those of men, the CHD death rates were much closer to those of men.

Impact of Cigarette Smoking on Coronary Heart Disease Mortality With Increasing Age

Coronary heart disease mortality increases with increasing age in both cigarette smokers and nonsmokers. The question of the magnitude of the CHD risk due to smoking for different age groups is one that has important public health impact for advising individuals at different ages about the risks of smoking and the benefits of cessation. In several of the prospective mortality studies, the question of the magnitude of the risk of dying of coronary heart disease at different ages in smokers and nonsmokers has been examined.

Table 9 details the coronary heart disease death rates and mortality ratios for different age groups of smokers and nonsmokers in each of the prospective studies reporting these data. As can be seen from this table, the CHD mortality ratios for cigarette smokers compared with nonsmokers decline with increasing age. However, the decline in the ratio is the result of the rapid rise in CHD mortality rates with age in nonsmokers, and the absolute difference between the death rates of cigarette smokers and nonsmokers increases with increasing age. Thus, the excess risk is actually numerically greater in older populations than in younger populations, and the reduction in mortality ratio is an artifact of the fact that coronary heart disease is responsible for such a large part of the mortality of the older age groups in the United States.

Figures 11 (men) and 12 (women) present the relationships of CHD mortality and age for nonsmokers and smokers of various number of cigarettes per day. The risk for the nonsmoker increases steadily with increasing age, but with each increment in number of cigarettes smoked per day, there is a clear increase in CHD risk prior to age 70. The shape of the curve with increasing age remains similar with increasing number of cigarettes smoked per day, and the net effect is consistent with cigarette smoking increasing the apparent "CHD risk age" of the individual by 5 to 15 years.

The decline in the mortality ratio with increasing age found in the prospective mortality studies is consistent with the risk factor relationships found in the incidence studies. In these studies, cigarette smoking is responsible for a relatively larger proportion of the coronary heart disease occurring in younger populations and a smaller percentage of the total coronary heart disease occurring in older populations.

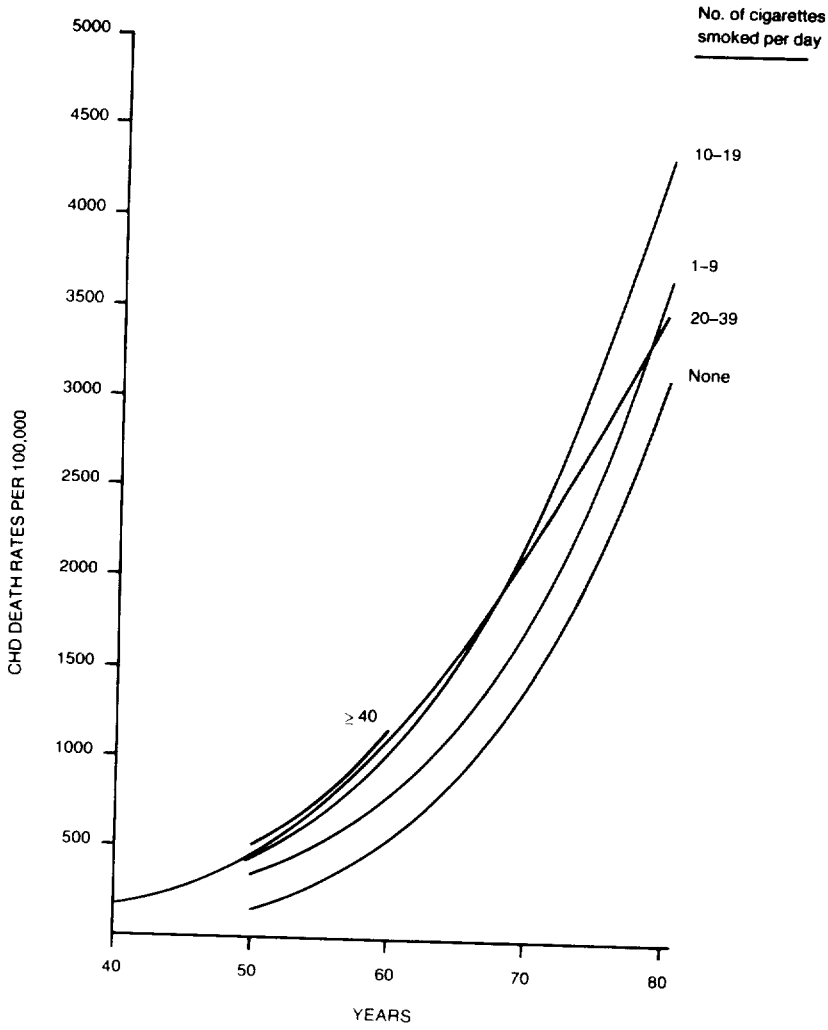

FIGURE 11.—CHD death rates (per 100,000), by age and number of cigarettes smoked per day, males

SOURCE: Derived from the ACS 25-State study (93).

Dose–Response Relationships

The large number of deaths observed in the prospective mortality studies allow a detailed examination of the relationship between the "dose" of smoke exposure and subsequent coronary heart disease mortality. The simplest measure of dose is the number of cigarettes smoked per day; however, the dose of smoke received by a person

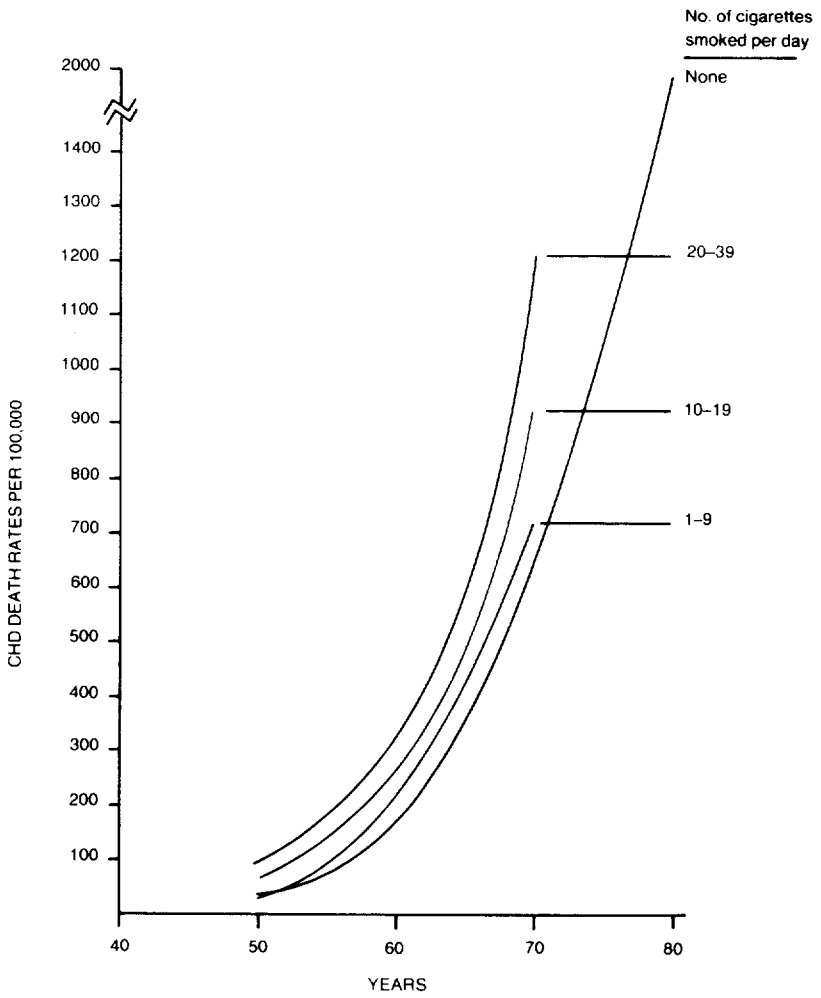

FIGURE 12.—CHD death rates (per 100,000), by age and number of cigarettes smoked per day, females

SOURCE: Derived from the ACS 25-State study (*93*).

would also be increased in those persons who inhaled deeply compared with those individuals who did not. The duration of the cigarette habit is also a measure of the dose of exposure; those persons who began to smoke earlier in life would have a greater cumulative exposure to cigarette smoke at any given age than those persons who began to smoke later in life. Several of the major prospective studies have examined these questions; the data are

TABLE 10.—Coronary heart disease mortality ratios by inhalation characteristic, prospective studies

Study	Sex	Age	Nonsmoker	Inhalation characteristic		
				Deep	Light	None
Swedish	Male		1.00	1.8	1.6	1.2
	Female		1.00	1.6	1.2	1.7[1]
				Yes	No	
British physicians	Male	<65	1.00	2.2	1.4	
		>65	1.00	1.5	1.3	
				None–slight	Moderate–deep	
ACS 25-State	Male	45–54	1.00	2.67	3.17	
		55–64	1.00	1.83	2.01	
		65–74	1.00	1.31	1.63	
		75–84	1.00	1.29	1.20	
	Female	45–54	1.00	1.82	2.15	
		55–64	1.00	1.61	1.89	
		65–74	1.00	1.30	1.78	
		75–84	1.00	1.13	—[2]	

[1] Number of deaths too small for statistical reliability.
[2] Number of deaths too small to compute.

presented in Tables 10, 11, and 12. Table 13 provides data from two studies that examined the risk of coronary heart disease mortality by length of time smoked. In general, they show that the more total years of smoking exposure the greater the overall risk of CHD mortality.

In the study of Canadian veterans, a progressive dose–response relationship was observed with number of cigarettes smoked per day. The CHD mortality ratio increased from 1.55 in those smoking 1 to 9 cigarettes per day to 1.78 among those who reported smoking 20 or more cigarettes per day. A similar relationship was found in the American Cancer Society 9-State study, where the excess CHD mortality rate varied from 29 percent in smokers of 1 to 9 cigarettes per day to 140 percent in smokers of 41 cigarettes or more per day.

In the American Cancer Society 25-State study, the number of CHD deaths was large enough to conduct a detailed examination of the relationship between the dose of cigarette smoke exposure and the subsequent coronary heart disease mortality. The mortality ratios for males in the group 45 to 54 years of age increased from 2.35 in those who smoked 1 to 9 cigarettes per day to 3.35 in those who smoked 40 or more cigarettes per day. In the next oldest age group, those 55 to 64 years of age, the mortality ratio increased from 1.54 in those who smoked 1 to 9 cigarettes per day to 2.13 in those who smoked 40 or more cigarettes per day (Table 14). The mortality ratio also increased with depth of inhalation. In the 45- to 54-year-old

TABLE 11.—Coronary heart disease mortality ratios by age began to smoke, prospective studies

Study	Age	Nonsmoker ratio	Smoker Mortality ratio by age of initiation			
U.S. veterans			≤14	15–19	20–24	≥25
	55–64	1.00	1.96	1.84	1.65	1.56
	65–74	1.00	2.03	1.66	1.54	1.55
ACS 25-State			≤14	15–24	≥25	
Males	45–54	1.00	3.47	3.11	2.37	
	55–64	1.00	2.08	1.99	1.70	
	65–74	1.00	1.54	1.62	1.17	
Females	45–54	1.00	—[1]	2.03	2.00	
	55–64	1.00	—	1.64	1.74	
	65–74	1.00	—	—	1.36	
Japanese			≤14	15–19	≥20	
Males		1.00	3.65	1.90	1.67	
Swedish			≤16	17–18	≥19	
Males		1.00	1.90	1.70	1.70	
Females		1.00	2.00	1.10	1.30	

[1] Number of deaths too small to calculate ratio.

age group, the mortality ratio increased from 2.67 in those who inhaled not at all or only very slightly to 3.17 in those who inhaled moderately or deeply (Table 10). There was also a consistent dose–response relationship when the age at which the individual started smoking was considered. The younger the age at which regular smoking began, the greater the mortality ratio. In the 45–54 age group the mortality ratio increased from 2.37 in those who began smoking at age 25 or older to 3.47 in those who began smoking prior to age 15 (Table 11).

For women, the excess mortality in the American Cancer Society 25-State study generally paralleled the dose–response relationship observed in men, but the CHD deaths were too few for evaluation of the risk related to the age at which smoking was begun.

A similar relationship was demonstrated in the study of California men in various occupations. The mortality ratio increased from 1.39 for those men who smoked half a pack per day to 1.74 for those who had smoked 1 1/2 packs or more per day. Mortality ratios increased with the duration of smoking from 1.05 in those who had smoked from 1 to 9 years to 1.77 in those who had smoked 20 years or more.

The study of British physicians also examined the question of a dose–response relationship. They found a steady increase in CHD mortality with increasing number of cigarettes smoked per day. The death rate from ischemic heart disease increased from 501 per 100,000 in those who smoked 1 to 14 cigarettes per day to 677 per

TABLE 12.—Coronary heart disease mortality ratios by amount smoked, prospective studies

Study	Males		Females	
	Cigs/day	Ratio	Cigs/day	Ratio
U.S. veterans	Nonsmoker	1.00		
	1–9	1.24		
	10–20	1.56		
	21–39	1.76		
	40+	1.94		
ACS 9-State	Nonsmoker	1.00		
	1–9	1.29		
	10–20	1.89		
	21–40	2.15		
	41+	2.41		
Japanese	Nonsmoker	1.00	(For female data, see Table 9)	
	1–14	1.59		
	15–24	1.79		
	25–49	2.11		
	50+	2.82		
ACS 25-State	Nonsmoker	1.00	(For female data, see Tables 9 and 14)	
	1–19	1.90		
	20+	2.55		
Canadian veterans	Nonsmoker	1.00		
	1–9	1.55		
	10–20	1.58		
	21+	1.78		
British physicians	Nonsmoker	1.00	Nonsmoker	1.00
	1–14	1.47	1–14	0.96
	15–24	1.58	15–24	2.20
	25+	1.92	25+	2.12
Swedish	Nonsmoker	1.00	Nonsmoker	1.00
	1–7	1.50	1–7	1.20
	8–15	1.70	8–15	1.60
	16+	2.20	16+	3.00
California occupations	Nonsmoker	1.00		
	about 1/2 pk	1.39		
	about 1 pk	1.67		
	about 1 1/2 pk	1.74		
Swiss physicians	Nonsmoker	1.00		
	1–10	1.33		
	10–19	1.42		
	29–34	1.77		
	35 or more	2.18		

100,000 in those who smoked 25 or more cigarettes per day. Depth of inhalation was analyzed after adjusting for age and amount smoked. Those responding that they did inhale experienced a 57 percent higher mortality rate than those responding that they did not inhale.

A dose–response relationship was also reported in the U.S. veterans study, the study of mortality in northeast England, the

TABLE 13.—Coronary heart disease mortality ratios by number of years having smoked, prospective studies

Study	Nonsmoker	Number of years having smoked							
		<5	5–9	10–14	15–19	20–29	30–39	≥40	
Canadian veterans	1.00	1.4	1.7	1.5	1.7	1.6	1.5	1.6	
		1–9		10–19			20+		
California occupations	1.00	1.05		1.13			1.77		

TABLE 14.—Coronary heart disease mortality ratios, males and females, by age and amount smoked, ACS 25-State study

Number of cigarettes/day	Age							
	45–54		55–64		65–74		75–84	
	M	F	M	F	M	F	M	F
Nonsmoker	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1–9	2.35	9.94	1.54	1.26	1.26	1.10	1.17	—[1]
10–19	3.09	2.00	1.92	1.64	1.61	1.42	1.39	—
20–39	3.11	2.67	2.04	2.01	1.56	1.85	1.11	—
40+	3.35	—	2.13	—	—	—	—	—

[1] Number of deaths too small to compute.

Swedish probability sample study, the Stockholm prospective study, and the study of 29 health districts in Japan. Mortality from CHD in the Whitehall study was higher in inhalers than in noninhalers, but the relative risk was reduced after adjusting for cigarette consumption and tar yield. Among inhalers, the risk increased with the amount smoked; this trend was less evident in those not inhaling.

Thus, in those studies that have had an adequate number of deaths to examine the question of a dose–response relationship between cigarette smoking and death from coronary heart disease, a clear dose–response relationship has been demonstrated for the number of cigarettes smoked per day, depth of inhalation, age at initiation of the smoking habit, and total duration of the smoking habit. The risk of coronary disease mortality is lower with fewer cigarettes smoked per day, but the evidence presented in the prospective mortality studies does not suggest a threshold for this effect. There is no evidence to suggest that any level of cigarette smoking is safe with regard to coronary heart disease risk.

Low Tar and Nicotine Cigarettes

There has been a major change in the tar and nicotine yield of the cigarettes being smoked by the U.S. population over the last 30 years. The impact of this decline in tar and nicotine yield on the risk of developing coronary heart disease in individuals smoking lower yield cigarettes has been examined in detail in the 1981 Report of the Surgeon General *The Health Consequences of Smoking: The Changing Cigarette* (*262*). There are essentially no epidemiological data on the risk of very low yield cigarettes (those below 5 mg of tar). The American Cancer Society 25-State study did, however, address the relative risk of those who smoked cigarettes with varying yields of tar (*95*). Groups were matched for age, race, number of cigarettes smoked per day, age at which smoking began, place of residence, occupational exposures, education, and history of lung cancer or heart disease. CHD mortality was calculated for two 6-year periods (1960–1966 and 1966–1972) for those smoking low, medium, or high tar and nicotine cigarettes. The men and women (both in early and late periods) who smoked cigarettes with high tar and nicotine yield experienced higher CHD death rates than those who smoked low tar and nicotine cigarettes (Table 15). Additional analyses were performed after further matching of the groups with respect to history of stroke; diabetes mellitus; hypertension; usual amount of exercise; obesity; consumption of aspirin, tea, coffee, and alcohol; and occupation. Although this procedure resulted in fewer matched subjects, the results were comparable to the analyses above; CHD mortality in the low tar and nicotine cigarette smokers was 86 percent of that of the high tar and nicotine cigarette smokers. However, this slight reduction in CHD mortality associated with smoking low tar and nicotine cigarettes disappeared if an increase in the number of cigarettes smoked per day occurred. Those smokers of low tar and nicotine cigarettes who smoke between 20 and 30 cigarettes per day experienced a 10 percent higher coronary heart disease mortality than did smokers of 1 to 19 high tar and nicotine cigarettes. In addition, a comparison of matched subjects who never smoked regularly with those who smoked low tar and nicotine cigarettes revealed that the low tar and nicotine cigarette smokers experienced a 66 percent higher coronary heart disease mortality rate.

Data from the Framingham study on the incidence of coronary heart disease (*30*) have not shown a lower CHD risk among filter smokers compared with nonfilter smokers.

Data from the Whitehall study have been published that examine tar yield by number of cigarettes smoked per day in inhalers and noninhalers for CHD mortality. This is presented in Table 16. While no clear pattern is evident for noninhalers, among inhalers there was a tendency for the highest CHD rates to be seen in those smoking cigarettes with the highest tar yield (*108*). In a recent study

TABLE 15.—Adjusted number of coronary heart disease deaths and mortality ratios during each of two periods of time, by sex and by tar and nicotine content of cigarettes usually smoked

Sex	Period[1]	High tar and nicotine	Medium tar and nicotine	Low tar and nicotine
		Adjusted number of CHD deaths		
Male	1	696.5	632.5	645.6
Male	2	336.0	345.6	274.2
Female	1	318.7	277.5	257.4
Female	2	265.6	228.0	215.5
Total		1,616.8	1,483.3	1,392.7
		Mortality ratios		
Male	1	1.00	0.91	0.93
Male	2	1.00	1.03	0.82
Female	1	1.00	0.87	0.81
Female	2	1.00	0.86	0.81
Total		1.00	0.92	0.86

[1] Period 1: 1960–1966; Period 2: 1966–1972.
SOURCE: Hammond et al. (95).

TABLE 16.—Ten-year coronary heart disease mortality per hundred (and number of deaths) standardized for age and employment grade, according to cigarette consumption and tar yield, Whitehall study

	Inhalers						Noninhalers					
	1–9/day		10-19/day		≥ 20/day		1-9/day		10–19/day		≥ 20/day	
Tar (mg/cig)	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.
18–23	2.68	(14)	5.63	(71)	6.60	(101)	3.94	(14)	4.91	(17)	6.05	(20)
24–32	3.81	(7)	6.57	(30)	6.23	(36)	1.78	(3)	9.03	(10)	4.27	(6)
≥ 33	7.42	(23)	6.47	(37)	7.84	(10)	5.08	(4)	4.75	(4)	0.00	(0)
Total	4.29	(44)	5.98	(138)	6.56	(147)	3.48	(21)	5.73	(31)	5.18	(26)

NOTE: Rate for lifelong nonsmokers of cigarettes = 2.75 (70).
SOURCE: Higgenbottam et al. (*108*).

(*140*), tar and nicotine content of the cigarettes was documented; those men who smoked low yield cigarettes did not have a lower risk for myocardial infarction than those smoking higher yield cigarettes.

The relative risk of developing coronary heart disease in persons smoking low yield cigarettes and persons smoking high yield cigarettes is further confounded by the possibility that those who

TABLE 17.—Coronary heart disease mortality ratios for male cigarette, pipe, cigar, and mixed pipe and/or cigar smokers, prospective studies

Study	Mortality ratios				
	Nonsmoker	Cigarette smoker	Pipe smoker	Cigar smoker	Mixed pipe and/or cigar smoker
U.S. veterans[1]	1.00	1.58	1.02	1.12	
ACS 9-State	1.00	1.70	—	1.28	
Swedish	1.00	1.70	1.40		
ACS 25-State[2]	1.00	1.90–2.55	1.08		
British physicians	1.00	1.62			1.03

[1] Smoker groups are "pure" smokers only.
[2] Age 55–84 only.

smoke low yield cigarettes may smoke greater numbers of cigarettes per day or may alter the manner in which they smoke those cigarettes to increase the yield from the cigarette. The available data are conflicting concerning a possible reduction in risk of CHD for those smoking the lower yield cigarettes; further evidence is needed before this question can be definitively answered.

Pipe and Cigar Smoking

A number of studies have addressed the question of the relative risk for CHD from smoking pipes and cigars compared with cigarettes. Those prospective mortality studies containing data that address this question are presented in Table 17. In general, the risk for coronary heart disease mortality of smoking pipes and cigars is substantially lower than the risk of smoking cigarettes. This is generally felt to be due to the tendency of pipe and cigar smokers not to inhale smoke into the lung. If this is the mechanism of this lower risk, then the tendency of those who switch from cigarettes to pipes and cigars to continue to inhale the smoke may minimize or eliminate the reduction in risk for coronary heart disease that might be expected after switching to pipes and cigars from cigarettes.

Cessation

Whether the excess coronary heart disease mortality that occurs with cigarette smoking decreases over time following cessation of cigarette smoking is a question of great importance for those individuals who are currently smoking cigarettes. Data from the prospective mortality studies that have examined this question are presented in Table 18.

TABLE 18.—Cessation of smoking and coronary heart disease mortality ratios, prospective studies

Study	Continuing smoker		Ex-smoker	
U.S. veterans	1.58		1.16	
Swedish males	1.70		1.50	
females	1.30		1.50	
ACS 25-State	1–19[1]	20+	1–19	20+
males	1.87	2.05	1.26	1.62
Canadian veterans	1.60		1.46	
British physicians males	1.62		1.29	
Japanese males in 29 health districts	1.71		1.34	

[1] Number of cigarettes smoked daily.

TABLE 19.—Cessation of smoking and CHD mortality ratios, by length of time off cigarettes and number of cigarettes smoked daily, ACS 25-State study, 6-year followup

Years stopped smoking	Amount smoked per day	
	1–19	20+
None, current smoker	1.87	2.05
Less than 1	2.00	2.13
1–4	1.43	2.00
5–9	1.44	1.45
10 or more	0.99	1.35
All ex-smokers	1.26	1.62

In the American Cancer Society 25-State study, the mortality ratios in former smokers compared with continuing smokers were progressively lower with increasing intervals of smoking cessation. For those who had smoked less than 20 cigarettes per day, the CHD mortality after 10 years of cessation was comparable with that of those who had never smoked regularly. However, for those who had smoked 20 or more cigarettes per day, the CHD mortality rate remained 35 percent higher even after 10 years (Table 19).

The British study of physicians also conducted a detailed analysis of the effects of cessation. The relative risk for males 30 to 54 years of age was 1.9 for those who had discontinued smoking for less than 5 years, but it was 1.3 for those who had discontinued smoking for 5 or more years. Those who discontinued smoking for 15 years or more had a relative risk that remained slightly above 1. Those aged 30 to

TABLE 20.—CHD mortality ratios by length of time off cigarettes

Study	Age	Mortality ratios: Nonsmoker	Years off cigarettes				Comments
			<5	5–9	10–14	5+	
British physicians (20-yr followup)	30–54	1.00	1.9	1.3	1.4	1.3	
	55–64	1.00	1.9	1.4	1.7	1.3	
	65+	1.00	1.0	1.3	1.2	1.1	
			<10		>10		
Swedish males (10-yr followup)		1.00	1.50		1.00		
			≤4		≥5		
Japanese males in 29 health districts (13-yr followup)		1.00	1.15		0.90		Smokers who consumed <200,000 cigarettes/ lifetime
		1.00	2.10		1.82		Smokers who consumed >200,000 cigarettes/ lifetime

64 had a relative risk of 1.3 after 15 years, while those 65 and over had a relative risk of 1.1 (Table 20).

The Swedish national probability sample study examined former smokers who had stopped in the 10 years prior to 1963. A relative risk of 1.6 existed for those who had smoked 20 years or more prior to quitting, but the relative risk was 0.9 for those who had smoked less than 20 years before quitting. Those at younger ages had greater residual relative risks than those in the older age groups. Among those who had stopped smoking 10 or more years prior to the beginning of the study, no significant excess risk of coronary disease was observed. The results in women were consistent with those in men, but the cases were too few for detailed analysis (Table 20).

In the Japanese study of 26 health districts, former smokers exhibited relative risks that were related inversely to the time since smoking cessation; the residual risk was directly proportional to the number of cigarettes smoked prior to quitting.

Data from the 16-year followup of U.S. veterans provides information on CHD mortality for ex-smokers by the number of cigarettes smoked per day (Table 21). Those ex-smokers with the lowest smoking exposure levels as measured by the number of cigarettes consumed per day had the lowest CHD mortality ratios. When all ex-smokers were analyzed by the length of time since cessation (Figure 13), ex-smokers who had been abstinent for 20 or more years had a CHD mortality ratio virtually identical to lifelong nonsmokers (1.00 versus 1.05). Friedman et al. (*69*) found that the benefits of quitting

TABLE 21.—Cessation of smoking and CHD mortality ratios of current smokers versus ex-smokers, by number of cigarettes smoked daily, U.S. veterans study, 16-year followup

No. cig/daily	Current smoker	Ex-smoker
Nonsmoker	1.00	1.00
1–9	1.24	1.02
10–20	1.56	1.14
21–39	1.76	1.31
40+	1.94	1.30
All smokers	1.68	1.16

SOURCE: Rogot and Murray (*224*).

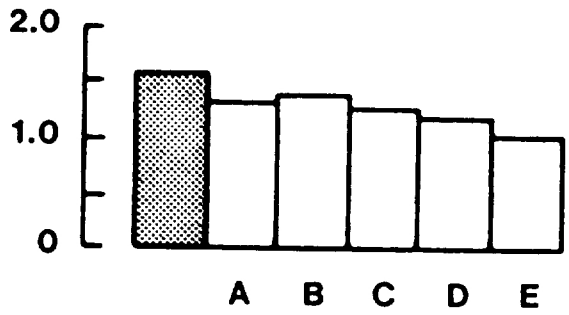

FIGURE 13.—Coronary heart disease mortality rates by number of years stopped smoking, U.S. veterans study, 16-year followup

NOTE: A = stopped less than 5 years; B = stopped 5–9 years; C = stopped 10–14 years; D = stopped 15–19 years; E = stopped 20 or more years.
SOURCE: Rogot and Murray (*224*).

smoking could not be explained by differences in other risk factor levels between continuing smokers and quitters.

Thus, cessation of cigarette smoking resulted in a reduction in the risk of CHD in each of the mortality studies that have examined the question. There appears to be some residual excess CHD risk in those ex-smokers who smoked heavily for extended periods of time prior to