CARDIOVASCULAR DISEASES.

CARDIOVASCULAR DISEASES

Introduction

While the mortality and morbidity rates of coronary heart disease (acute myocardial infarction and chronic ischemic heart disease) (CHD) are lower for women than men, CHD still represents the major cause of death among women in the U.S. In 1976 the United States recorded 284,055 female deaths as attributable to this cause (Table 2). The difference in mortality rates between the sexes is more marked for acute myocardial infarction, with males of all ages experiencing 189 deaths and females 111 deaths per 100,000 (Table 1). Observed differences by sex in susceptibility to coronary heart disease are not fully understood but appear to be affected by multiple specific risk factors within any demographic group.

McGill and Stern have recently provided an extensive review of sex differences in susceptibility to atherosclerosis in humans and in experimental animals, including an analysis of factors known to predispose to atherosclerosis and its dependent diseases (25).

Mortality Rates

In the United States, the National Center for Health Statistics has reported mortality rates from acute myocardial infarction and chronic ischemic heart disease classified by age, sex, and race, for the years 1968 and 1976 (Tables 1–3) (33). These tables show that mortality rates for acute myocardial infarction among adults up to age 64 are highest for white men and are succeeded by progressively lower rates for other men, other women, and finally, white women. Mortality rates for chronic ischemic heart diseases vary. The rates for white men are second to those for other men and close to those for nonwhite women; again, however, rates for white women are by far the lowest. Both white and nonwhite women show consistently lower rates until extreme old age. However, the differences narrow markedly in age in comparison with those in young adulthood and middle life (Table 1).

Male-to-female mortality ratios for acute myocardial infarction among adults in their 30's and 40's are approximately 5 to 6 for whites and 2 to 3 for nonwhites; among adults in their 70's and 80's, they are roughly 1.6 and 1.4. The actual number of deaths involved is very large; their distribution by age, sex, and race is shown in Table 2. Between 1968 and 1976, a striking decline occurred in the acute myocardial infarction mortality rate for men and women of all ages and races. These are shown

TABLE 1.—Death rates* for acute myocardial infarction and chronic ischemic heart disease for specified age groups, by color and sex; United States, 1968–1976

Year and age	Total			White			All Other		
	Both sexes	Male	Female	Both sexes	Male	Female	Both sexes	Male	Female
1976				Acute myocardial infarction					
All ages	148.8	189.0	110.8	158.7	202.2	117.3	84.0	100.3	69.0
25–34 years	2.8	4.6	1.1	2.6	4.3	0.9	4.2	6.4	2.3
35–44 years	27.0	46.2	8.8	26.6	46.1	7.6	30.4	47.5	10.3
45–54 years	111.7	186.9	41.3	111.8	190.1	37.7	111.2	159.8	68.9
55–64 years	309.5	490.3	147.2	312.2	501.1	142.1	283.2	386.5	194.8
65–74 years	660.1	989.8	406.8	674.5	1,024.7	406.5	524.6	667.9	409.9
75–84 years	1,328.0	1,806.7	1,035.7	1,364.8	1,881.4	1,054.3	917.0	1,061.1	813.0
85 years and over	2,038.0	2,564.7	1,790.3	2,135.0	2,709.6	1,869.9	1,126.5	1,369.1	990.1
1968									
All ages	185.4	243.0	130.6	195.9	258.0	136.7	109.5	133.2	87.7
25–34 years	4.6	7.2	2.2	4.1	6.5	1.7	8.7	13.1	5.0
35–44 years	42.3	70.9	15.2	40.3	69.6	12.1	57.9	81.6	37.9
45–54 years	158.5	267.1	56.8	157.6	270.4	51.3	166.6	236.2	105.3
55–64 years	420.8	668.3	197.1	423.9	684.3	188.4	390.5	512.5	281.0
65–74 years	900.5	1,315.0	574.1	919.8	1,360.8	574.4	706.7	870.1	571.2
75–84 years	1,687.1	2,228.4	1,316.5	1,732.1	2,306.5	1,342.8	1,103.1	1,291.4	961.1
85 years and over	2,911.8	3,570.7	2,553.0	3,012.9	3,715.3	2,637.8	1,782.4	2,163.4	1,526.2

TABLE 1.—Death rates* for acute myocardial infarction and chronic ischemic heart disease for specified age groups, by color and sex; United States, 1968–1976—(Continued)

Year and age	Total Both sexes	Male	Female	White Both sexes	Male	Female	All Other Both sexes	Male	Female
1976	—			Chronic ischemic heart disease					
All ages	150.2	153.5	147.0	155.5	157.7	153.4	115.4	125.4	106.4
25–34 years	1.6	2.4	0.8	1.2	1.9	0.5	4.2	6.1	2.5
35–44 years	12.8	20.3	5.6	10.6	17.5	3.9	27.5	41.0	16.3
45–54 years	57.7	90.9	26.7	50.4	82.6	20.1	116.1	160.7	77.4
55–64 years	173.3	258.5	96.8	159.5	244.3	83.2	302.2	396.1	222.0
65–74 years	487.4	674.8	343.4	467.8	660.5	320.4	672.1	805.8	565.2
75–84 years	1,621.5	1,947.4	1,422.6	1,626.0	1,968.0	1,420.4	1,572.0	1,742.7	1,448.8
85 years and over	4,647.4	4,945.8	4,507.0	4,859.8	5,208.0	4,699.1	2,650.8	2,782.4	2,576.9
1968									
All ages	150.6	156.3	145.1	153.1	158.3	148.2	132.0	141.6	123.3
25–34 years	1.6	2.3	1.1	1.0	1.6	0.4	6.2	7.2	5.3
3Γ–44 years	13.6	20.5	7.1	10.4	17.0	4.0	38.8	49.8	29.5
45–54 years	57.0	85.6	30.2	47.5	76.0	20.7	142.6	175.8	113.3
55–64 years	190.6	273.4	115.7	169.2	253.4	93.0	393.1	468.6	334.8
65–74 years	590.4	769.1	449.7	560.6	742.8	417.9	889.5	1,025.0	777.2
75–84 years	1,826.0	2,075.5	1,655.3	1,833.9	2,093.7	1,657.8	1,724.6	1,858.1	1,628.0
85 years and over	5,523.6	5,636.6	5,468.4	5,695.3	5,831.8	5,629.4	3,605.9	3,736.6	Ϩ518.0

*Rates are deaths per 100,000 population. For acute myocardial infarction, rates are based on deaths assigned to category number 410 of the Eighth Revision of the International Classification of Diseases, adapted for use in the United States, adopted in 1965, and for chronic ischemic heart disease, to category number 412 of this revision

SOURCE: Rosenberg, H.M. (33).

TABLE 2.—Number of deaths* for acute myocardial infarction and chronic ischemic heart disease for specified age groups, by color and sex; United States, 1968 and 1976

Year and age	Total			White			All other		
	Both sexes	Male	Female	Both sexes	Male	Female	Both sexes	Male	Female
1976				Acute myocardial infarction					
All ages	319,477	197,429	122,048	295,613	183,820	111,793	23,864	13,609	10,255
25–34 years	890	718	172	720	598	122	170	120	50
35–44 years	6,223	5,182	1,041	5,338	4,558	780	885	624	261
45–54 years	26,405	21,361	5,044	23,479	19,407	4,072	2,926	1,954	972
55–64 years	62,091	46,516	15,575	56,623	43,072	13,551	5,468	3,444	2,024
65–74 years	93,695	61,038	32,657	86,566	57,004	29,562	7,129	4,034	3,095
75–84 years	89,969	46,395	43,574	84,852	43,912	40,940	5,117	2,483	2,634
85 years and over	40,068	16,132	23,936	37,939	15,201	22,738	2,129	931	1,198
1968									
All ages	369,610	236,017	133,593	342,999	220,517	122,482	26,611	15,500	11,111
25–34 years	1,099	838	261	846	664	182	253	174	79
35–44 years	9,980	8,132	1,848	8,412	7,122	1,290	1,563	1,010	558
45–54 years	36,032	29,368	6,664	32,261	26,860	5,401	3,771	2,508	1,263
55–64 years	76,108	57,387	18,721	69,504	53,287	16,217	6,604	4,100	2,504
65–74 years	109,672	70,564	39,108	101,863	66,205	35,658	7,809	4,359	3,450
75–84 years	100,312	53,838	46,474	95,613	51,436	44,177	4,699	2,402	2,297
85 years and over	36,135	15,711	20,424	34,317	14,824	19,493	1,818	887	931
1976				Chronic ischemic heart disease					
All ages	322,382	160,375	162,007	289,572	143,372	146,200	32,810	17,003	15,807
25–34 years	502	381	121	332	266	66	170	115	55
35–44 years	2,937	2,273	664	2,137	1,734	403	800	539	261

Year and age	Total			White			All other		
	Both sexes	Male	Female	Both sexes	Male	Female	Both sexes	Male	Female
45–54 years	13,649	10,391	3,258	10,593	8,426	2,167	3,056	1,965	1,091
55–64 years	34,765	24,525	10,240	28,929	20,996	7,933	5,836	3,529	2,307
65–74 years	69,176	41,612	27,564	60,042	36,745	23,297	9,134	4,867	4,267
75–84 years	109,860	50,010	59,850	101,088	45,932	55,156	8,772	4,078	4,694
85 years and over	91,368	31,109	60,259	86,358	29,217	57,141	5,010	1,892	3,118
1968									
All ages	300,216	151,815	148,401	268,124	135,333	132,791	32,092	16,482	15,610
25–34 years	390	262	128	211	166	45	179	96	83
35–44 years	3,212	2,350	862	2,162	1,734	428	1,050	616	434
45–54 years	12,953	9,412	3,541	9,727	7,545	2,182	3,226	1,867	1,359
55–64 years	34,475	23,481	10,994	27,743	19,732	8,011	6,732	3,749	2,983
65–74 years	71,905	41,270	30,635	62,076	36,135	24,941	9,829	5,135	4,694
75–84 years	108,576	50,145	58,431	101,229	46,689	54,540	7,347	3,456	3,891
85 years and over	68,548	24,801	43,747	64,870	23,269	41,601	3,678	1,532	2,146

*Number of deaths due to acute myocardial infarction are those assigned to category number 410 of the Eighth Revision of the International Classification of Diseases, adapted for use in the United States, adopted in 1965; and for chronic ischemic heart disease to category number 412 of this revision

SOURCE: Rosenberg, H.M. (33).

as percent changes in rate in Table 3. The percent change has been larger at younger ages (Tables 2 and 3). The changes for chronic ischemic heart disease are similar but less dramatic (Table 3).

Atherosclerosis

Differences in heart attack mortality rates among men and women parallel pathology data concerning atherosclerotic plaques of the coronary arteries. The International Atherosclerosis Project systematically collected autopsy observations on persons from 14 geographic locations and 19 ethnic groups in different parts of the world, and found that women from 11 of the 19 groups, when compared to their male counterparts, had as much or even more aortic atherosclerosis. Men over age 39 had more raised plaques in their coronary arteries than women (24).

These findings indicate that the occurrence of coronary plaques was parallel to heart attack rates, but that the occurrence of aortic lesions was not. Coronary plaque severity had a male-to-female ratio of 1.61 among whites and of 1.14 among blacks. Studies of a white population in Sweden (40) and of western Europeans from five locations (18) demonstrate similar findings: a clear excess of coronary atherosclerosis among men and a similar severity of aortic atherosclerosis among men compared to women.

Autopsy studies thus show a selective liability of the male coronary arterial bed for atherosclerosis, as compared to the female, especially among white men but also among men of other races. The pathological findings are congruent with the clinical data on heart attack mortality rates. Autopsy studies also show that, among men or women with manifest coronary heart disease, women patients have roughly the same prevalence of advanced atherosclerotic lesions of the coronaries as men (41). These data suggest that the amount of atherosclerosis necessary to precipitate a heart attack is the same, on the average, in both sexes. This generalization about the amount of coronary atherosclerosis appears to hold for heart attacks at younger and older ages, for recent and old infarcts, and coronary occlusion without infarct, and for stenosis, as well as for complicated and calcified lesions and raised plaques in the coronary arteries (41).

It should be noted that the grading of atherosclerosis at autopsy is not a simple matter because there are several types of lesions and several ways of evaluating or measuring them. Moreover, the development of the different sorts of lesions is

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TABLE 3.—Percent change* between 1968 and 1976 in death rates for acute myocardial infarction and chronic ischemic heart diseases for specified age groups, by color and sex: United States

Age	Total			White			All Other		
	Both Sexes	Male	Female	Both Sexes	Male	Female	Both Sexes	Male	Female
Acute myocardial infarction									
All ages	−19.7	−22.2	−15.2	−19.0	−21.6	−14.2	−23.3	−24.7	−21.3
25–34 years	−39.1	−36.1	−50.0	−36.6	−33.8	−47.1	−51.7	−51.1	−54.0
35–44 years	−36.2	−34.8	−42.1	−34.0	−33.8	−37.2	−47.5	−41.8	−57.0
45–54 years	−29.5	−30.0	−27.3	−29.1	−29.7	−26.5	−33.3	−32.3	−34.6
55–64 years	−26.4	−26.6	−25.3	−26.4	−26.8	−24.6	−27.5	−24.6	−30.7
65–74 years	−26.7	−24.7	−29.1	−26.7	−24.7	−29.2	−25.8	−23.2	−28.2
75–84 years	−21.3	−18.9	−21.3	−21.2	−18.4	−21.5	−16.9	−17.8	−15.4
85 years and over	−30.0	−28.2	−29.9	−29.1	−27.1	−29.1	−36.8	−36.7	−35.1
Chronic ischemic heart diseases									
All ages	−0.3	−1.8	1.3	1.6	−0.4	3.5	−12.6	−11.4	−13.7
25–34 years		4.3	−27.3	20.0	18.8	25.0	−32.3	−15.3	−52.8
35–44 years	−5.9	−1.0	−21.1	1.9	2.9	−2.5	−29.1	−17.7	−44.7
45–54 years	1.2	6.2	−11.6	6.1	8.7	−2.3	−19.6	−8.6	−31.7
55–64 years	−9.1	−5.4	−16.3	−5.7	−3.6	−10.5	−24.1	−15.5	−33.7
65–74 years	−17.4	−12.3	−23.6	−16.6	−11.1	−23.3	−24.4	−21.4	−27.3
75–84 years	−11.2	−6.2	−14.1	−11.3	−6.0	−14.3	−8.8	−6.2	−11.0
85 years and over	−15.9	−12.3	−17.6	−14.7	−10.7	−16.5	−26.5	−25.5	−26.8

*Percent changes are based on rates per 100,000 population. For 1968 and 1976, rates for acute myocardial infarction are based on deaths assigned to category number 410 of the Eighth Revision of the International Classification of Diseases, adapted for use in the United States, adopted in 1965, and for chronic ischemic heart disease, on category number 412 of this revision

SOURCE: Rosenberg, H.M. (33).

not necessarily parallel. Sternby provides a useful discussion of issues in the grading of atherosclerosis (40). Nevertheless, the major studies noted above provide strong evidence that women have less coronary atherosclerosis on the average than men of the same age in the same population

Risk Factors

Factors present in individuals which correlate with future liability to disease are risk factors for that disease. In the case of heart attack, for example, it has been shown that age, male sex, cigarette smoking, hypertension, elevated blood cholesterol, and several other conditions are positively and independently associated with the probability of heart attack. The level of high-density lipoprotein cholesterol in the serum has a negative correlation with heart attack; that is, higher levels are protective. The various risk factors have been identified for both men and women and have been shown on multivariate analysis to be independent. A combination of risk factors is synergistic, producing an associated risk greater than the simple sum of the individual risks. Although the data for women are much less extensive than for men, they indicate that cigarette smoking is a major risk factor for heart attack in women.

The Effect of Smoking

ATHEROSCLEROSIS

There is little autopsy information about the amount of atherosclerosis in women smokers. Sackett and his associates reported on aortic atherosclerosis among both men and women: of their 450 female subjects, 309 were nonsmokers, 52 smoked less than a half pack per day, and 89 smoked more (34). Mean, age-adjusted aortic atherosclerosis was found to increase in conjunction with the amount and duration of smoking.

A study of the intramyocardial arteries and arterioles of the heart in 13 women and 21 men who were nonsmokers, and 16 women and 27 men who were smokers, indicated that proliferative lesions in intramyocardial arteries were more advanced relative to age in smokers than nonsmokers. It was also found that subendocardial arterioles were thickened in smokers. A separate analysis by sex was not performed, but the authors remarked that the lesions developed as rapidly and as extensively in women as in men in both smoking and nonsmoking groups (28).

Studies of the severity of atherosclerotic plaques in the arteries of women who smoked in comparison with those who did

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TABLE 4.—Coronary heart disease mortality ratios related to smoking—prospective study

Author, year, country	Number and type of populations	Data collection	Follow-up (years)	Number of deaths	Cigarettes/day			Age Variation			
Hammond and Garfinkel, 1969, U.S.A.	358,584 males 445,875 females age 40–70 at entry.	Questionnaire and follow-up of death certificate	6	14,819		M	F				

Cigarettes/day:

	M	F
NS	1.00	1.00
1–9	1.27	0.81
10–19	1.00	1.22
20–30	1.75	1.52
>40	1.77	0.61

Age Variation — Males:

	40–49	50–59	60–69	70–79
NS	1.00	1.00	1.00	1.00
1.9	1.00	1.50	1.48	1.14
10–19 ...	2.39	2.13	1.82	1.41
20–30 ...	3.76	2.40	1.91	1.49
>40	3.51	2.79	1.71	1.47

Age Variation — Females:

	40–49	50–59	60–69	70–79
NS	1.00	1.00	1.00	1.00
1.9	1.31	1.15	1.04	0.74
10–19 ...	2.04	2.37	1.79	0.98
20–30 ...	3.62	2.69	2.00	1.27
>40	+3.31	3.73	+2.02	

Based on 5–9 deaths
NS = nonsmokers, M = males, F = females
SOURCE: U.S. Public Health Service (44,45).

not smoke involve too few subjects to be satisfactory. Investigating the relationship of these arterial lesions and cigarette smoking in women is fundamental to understanding the occurrence of heart attack and other ischemic diseases.

CORONARY HEART DISEASE

Coronary heart disease (acute myocardial infarction and chronic ischemic heart disease) occurs with greater frequency in smoking than in nonsmoking women. The prospective study of Hammond and Garfinkel, published in 1969, included data on approximately 446,000 women between the ages of 40 and 79 (10). The increase in mortality ratios in conjunction with increasing numbers of cigarettes smoked per day for various ages is shown below in Table 4 (43,44). Mortality ratios were higher for younger ages and lower for older ages. The one-pack-a-day smoker's risk of death from heart attack was approximately twice that of the nonsmoker. The prospective data of Shapiro and colleagues are based on a population of 120,000 men and women (36). Using a sampling factor of about one-thirtieth, they examined 4,301 women at risk of a first myocardial infarction between the years 1962 and 1964. The smokers compared with nonsmokers had roughly twice as many rapidly fatal heart attacks and heart attacks that were not fatal within 48 hours. The ratio was approximately 2.9 among younger women aged 45 to 54 and 1.8 for the subjects aged 55 to 64. Heavy smokers had higher ratios, but the data did not permit a detailed study of dose relationships or of the experience of female ex-smokers.

A recent study examined the cause-specific mortality of 6,194 British women physicians over the period 1951 to 1973 (6). Table 5 presents the results of this study in conjunction with the previously published results among male physicians during the same period (7). The clear association of cigarette smoking and ischemic heart disease previously described in males was confirmed in female physicians. For women who reported smoking 15 or more cigarettes per day, mortality due to ischemic heart disease was more than double that of nonsmokers.

Although the results demonstrated a similar effect of smoking in the development of ischemic heart disease in both male and female physicians, the association of smoking with heart disease was less striking in women physicians. Ischemic heart disease was less prominent as a proportional cause of death in this population of women than in male colleagues (16 percent vs. 32 percent of all deaths). Ischemic heart disease mortality was only 26 percent higher for all ever-smoked women than for never-smoked women. However, for females who smoked heav-

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TABLE 5.—Death from ischemic heart disease and smoking habits when last asked, British physicians 1951–1973

| | Total Popul. | Number of Deaths | Annual Death Rate per 100,000 Persons Standardized for Age | | | | | X^2 | |
| | | | | | Current Smokers - Dose Per Day | | | Nonsmokers vs. others | Trend |
			Nonsmokers	Ex-smokers	1-14	15-24	> 25		
Women	6194	179	138	126	132	304	292	...	21.14*
					(number of cigarettes)				
Men	34,440	3191	413	533	501	598	677	22.59*	53.56*
					(any tobacco—grams) (1 gram = 1 cigarette)				

*P < 0.001.
SOURCE: Doll, R. (6,7).

ily (≥ 25 cigarettes per day), the relative risk of death from ischemic heart disease was 2.2, a finding consistent with that demonstrated in males, who had a relative risk of 1.6.

In such studies, standardization for amount smoked daily by each of the sexes does not, however, correct for differences in age at initiation of smoking and degree of inhalation. This fact greatly complicates comparison of the magnitude of biologic effect in the two sexes. This "cohort effect" (i.e., unmeasured but documented dissimilarities in total smoking experience) may lead to an erroneous interpretation that cigarette smoking is less damaging to women than to men. This issue cannot be resolved until studies examine the effect of smoking in more recent cohorts of women whose lifetime smoking behavior is more similar to that of men.

Among 26,467 Swedish women observed during a 10-year period, the risk of developing fatal coronary heart disease was significantly higher among smokers than nonsmokers (50). The relative risk was 1.9 at ages 40 to 49 and 1.3 at ages 50 to 59. An extensive mortality study in Japan also reported a highly significant increase in deaths from ischemic heart disease among female smokers, with a mortality ratio for smokers of 1.6 (29).

Coronary heart disease morbidity data are available on women from prospective studies in Framingham, Massachusetts, Tecumseh, Michigan, and the greater New York areas. The Tecumseh data of 1967 do not show a relationship of such morbidity with smoking (Table 6) (8). The Framingham Heart Study found an increased risk for women smokers, but the associations were weak (19,20).

The study of Shapiro and colleagues considered both mortality and morbidity (36). It reported separately on deaths within 48 hours of onset and on all definite myocardial infarctions after that time interval. Using this classification, the incidence of coronary heart disease among women smokers was distinctly higher than it was among nonsmokers.

While there is some variability in the strength of this association, the data from the various prospective studies of mortality and morbidity from coronary heart disease establish smoking as a positive correlate, or risk factor, for women. However, the risk ratios tend to be smaller than for men at a given level of cigarette consumption in all age groups. This trend may result from the different smoking patterns reported by men and women who smoke the same number of cigarettes per day (6,7,25). Men generally begin smoking at an earlier age and have thus smoked for a longer time period than women. Men also inhale more often than women and are more likely to smoke more than half of a cigarette. These smoking styles would ex-

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TABLE 6.—Coronary heart disease morbidity as related to smoking

Author, year, country	Number and type of population	Data collection	Follow-up years[1]	Number of incidents[2]	Cigarettes/day[3]			Pipes, cigars	
Epstein, 1967, U.S.A.	6,568 male and female residents of Tecumseh, Mich.	Initial medical examination and repeat follow-up examinations.	4	96 male, 92 female CHD including deaths, angina, and myocardial infarctions	Males			Males	
						40–59	60 and over	40–59	
					NS	1.00 (1)	1.00 (7)	SM 1.80 (2)	
					EX	6.33 (10)	1.27 (11)		
					Cigarettes	5.20 (36)	1.90 (23)	60 and over	
								SM 0.80 (6)	
					Females				
						40–59	60 and over		
					NS	1.00 (21)	1.00 (47)		
					EX	0.89 (3)	1.31 (5)		
					Cigarettes	1.02 (14)	0.42 (2)		

[1]Reexamination of patients was spread over 1½–6 year period, but data are reported in terms of 4-year incidence rates.
[2]Actual number of CHD incidents derived from data on incidence and total in smoking class.
[3]Risk ratios—actual number of CHD incidents shown in parentheses. SM = smokers, NS = nonsmokers, EX = ex-smokers.
SOURCE: U.S. Public Health Service (45).

pose men to a larger dose of smoke per cigarette and a larger lifetime amount than that experienced by women.

Case control and retrospective studies of women who have had heart attacks have suggested an increased incidence of heart attack among smokers. For example, a case control study of 55 women who had heart attacks before age 50 (an uncommon event in women) found that 89 percent were smokers in contrast to 55 percent in a control group without myocardial infarction. Heavy smokers (35 or more cigarettes per day) had an estimated myocardial infarction rate approximately 20 times that of the nonsmokers. As far as possible, women using oral contraceptives and those with other identifiable risk factors were excluded from the study (37).

Spain and his associates conducted a retrospective autopsy study of women who had died suddenly of coronary heart disease and compared this verified diagnosis to the women's smoking habits as reported by the closest living relative (38). Only witnessed sudden deaths were included in the data. Comparisons were made between women who had died of coronary heart disease and women who died suddenly of causes other than heart attack. It was found that 62 percent of the women suffering sudden cardiac death were heavy smokers in contrast with only 28 percent of the control group. For those who smoked heavily, the mean age at death was 19 years younger than that of nonsmokers; lighter smokers died at an intermediate mean age.

In a retrospective study emphasizing psychosocial variables, Talbott and associates reported on 64 white women who died suddenly of arteriosclerotic heart disease (42). They found that women who died suddenly smoked more cigarettes than the comparison group. The relative risk for those smoking more than a pack a day compared with those smoking less than a pack a day was 3.9 ($p < .004$).

Smoking, as well as other risk factors, raises the already somewhat higher risk of myocardial infarction among women who use oral contraceptives. During the child-bearing years, the use of oral contraceptives doubles the risk of myocardial infarction; women who both smoke and use oral contraceptives have approximately 10 times the risk of women who neither smoke nor use oral contraceptives (14). These issues are considered below in a separate section.

Cessation of Smoking and "Tar" and Nicotine Content of Cigarettes

Existing data are inadequate to determine the effect of smoking cessation on the incidence of coronary heart disease in

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women. Hammond and associates have reported that mortality rates from coronary heart disease were lower in women who smoked low-"tar" and low-nicotine cigarettes (as sold in the 1960s) than in those who smoked medium level products, and still lower than for those who smoked high-"tar" and high-nicotine products; even so, the mortality rate for those women smoking low-"tar", low-nicotine products was significantly higher than that of nonsmokers (11).

Evidence considered below suggests that stopping smoking is beneficial in the treatment of women suffering from peripheral vascular disease.

ANGINA PECTORIS

The Framingham Heart Study reported that there was a positive association between smoking and angina pectoris among men but not among women (20). In an extensive study conducted in New York City, Shapiro and colleagues reported a positive association between the development of angina pectoris and smoking among men and a nonsignificant positive trend among women (37). Among patients with angina pectoris, smoking lowers the exercise threshold for the onset of angina (46). Only male patients have been studied thus far; equivalent data apparently have not been published for women with angina and angiographically proven coronary atherosclerosis.

CEREBROVASCULAR DISEASE

The incidence of stroke as a manifestation of cerebrovascular disease appears to be somewhat greater in men than in women, but the difference is small (21,30,43).

In an autopsy assessment of cerebrovascular atherosclerosis, Sternby reported more atherosclerosis of the common carotid artery and the carotid sinus in men than women. There was also more intracranial atherosclerosis of certain vessels in men than women. However, using the area-grading method, no sex difference was found in total intracranial atherosclerosis (40). The International Atherosclerosis Project also reported a slight excess of cerebrovascular atherosclerosis among males (24). On the whole, the available pathological evidence suggests a minor increase in cerebrovascular atherosclerosis among men in comparison with women, although some studies fail to confirm this conclusion (see 40).

It is not clear whether smoking is a risk factor among women for the development of atherothrombotic stroke. Kannel has discussed the issue and the current literature in some detail (19). The Framingham Heart Study has reported a dose-related

TABLE 7.—Deaths from cerebrovascular disease related to smoking

Author, year, country	Number and type of population	Data collection	Follow-up years	Number of deaths due underlying to CVD as cause	Mortality ratios			
Hammond and Garfinkel, 1969, U.S.A.	358,584 males 445,875 females 40–79 years of age at entry.	Questionnaire and follow-up of death certificate	6	4,099			Age	
					Cigarettes/day	40–49	50–59 60–69	70–79
							Males	
					Never smoked	1.00	1.00 1.00	1.00
					1–9	2.79	1.95 1.30	0.95
					10–19	1.14	1.48 +1.44	0.92
					20–30	2.21	2.03 1.62	1.22
					>40	1.64	2.40 1.72	+0.68
							Females	
					Never smoked	1.00	1.00 1.00	1.00
					1–9	1.50	1.26 1.26	0.83
					10–19	2.60	2.70 2.15	+0.57
					20–30	2.90	2.67 1.83	1.28
					> 40	+5.70	+3.52 —	—

SOURCE: U.S. Public Health Service (44,45).

correlation between the incidence of atherothrombotic stroke and cigarette smoking in men but not in women. The extensive prospective study of Hammond and Garfinkel, which involved almost 446,000 women and recorded 1,905 deaths from cerebrovascular disease during a six-year period, found that smoking was a positive correlate for such mortality (10); in both men and women, the mortality ratio was increased by roughly 2 or 2.5 times (Table 7) (44,45).

That some of these deaths may have involved subarachnoid hemorrhage rather than brain infarction, is suggested by a recent report that found the incidence of subarachnoid hemorrhage to be positively associated with smoking for both men and women (2). The relative risk for men was 3.9 and for women, 3.7. The association appeared to relate to hemorrhage from ruptured cerebral aneurysms rather than to other conditions that may give rise to subarachnoid hemorrhage. A synergism between smoking and the use of oral contraceptives and subarachnoid hemorrhage is noted below (31). The Japanese study cited in the discussion of ischemic heart disease has also reported on 366 deaths from cerebrovascular disease among women who smoked (29). The risk ratios for subarachnoid hemorrhage and cerebral hemorrhage were both significantly increased among women smokers (p<.001) as was the risk rate for the category, "other forms of cerebrovascular disease" (p<.05).

ARTERIOSCLEROTIC PERIPHERAL VASCULAR DISEASE

Clinicians have noted that arteriosclerotic peripheral vascular disease is more common in men than women. Sternby has reported from autopsy studies that men generally have somewhat more atherosclerosis of the femoral and pelvic arteries than women (40).

Kannel has reviewed the relationship of smoking to the incidence of arteriosclerotic peripheral vascular disease (19). In the Framingham Heart Study the incidence of peripheral vascular disease was increased among smokers of both sexes; cigarette smoking was as strong an independent risk factor in women as in men. Heavy smokers had a threefold increased incidence.

Weiss studied 245 women with arteriosclerotic peripheral vascular disease (49). Ex-smokers who had not smoked for 5 years or more had nearly a normal risk ratio of 1.06; those who had not smoked for the last 1 to 5 years had a risk of 1.70; continuing smokers of less than a pack a day, 5.15; pack a day smokers, 11.53; and those smoking more than a pack a day, 15.56 (relative to nonsmokers, 1.00). The increased risk was particu-

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larly associated with proximal (aortoiliac) disease, and there was less association with distal (femoropopliteal) disease. Age-standardized relative risk ratios for those smoking a pack a day were 30.06 for proximal and combined proximal and distal disease and 6.32 for distal disease alone.

A retrospective study of 217 patients who underwent arterial reconstructive procedures of various kinds for peripheral vascular disease has been reported by Myers and colleagues (27). Diabetics were excluded from the report. There were 164 male and 53 female patients. The late patency rate of the vascular reconstruction was followed for 1 to 4 years. The authors reported that the number of cigarettes smoked before surgery did not influence the outcome, but cessation of smoking after surgery had a favorable impact. There were no significant differences in outcome between men and women. The patency rate 4 years after aortofemoral surgery was 90 percent in those who smoked five or fewer cigarettes per day after surgery and 75 percent in those who smoked a greater amount. Following femoropopliteal reconstruction, the 2-year patency rates were 95 percent for those who stopped smoking, 75 percent for those smoking as many as 15 cigarettes per day, and 65 percent for those who continued to smoke more than 15 cigarettes per day.

AORTIC ANEURYSM

Studies have not been reported for women with respect to atherosclerotic aortic aneurysm and smoking. Deaths for women are about one-fifth those for men (10).

HYPERTENSION

Smoking is not associated with an increased prevalence of essential hypertension in men or women (39). However, smoking does combine with hypertension (and other risk factors) as a risk factor for heart attack, synergistically compounding the risk.

Two recent case control studies of rapidly progressive, severe or malignant hypertension have found that there is an overrepresentation of smokers among patients with this uncommon phase of hypertension (3,13). In one study of 82 patients who developed malignant hypertension, 67 were smokers. Thirty-three of those were women. In the study, 77 percent of the female patients with malignant hypertension smoked, and only about 44 percent of those with essential hypertension and of the general female population smoked. The difference is highly significant. A similar and parallel study of 48 patients with malignant hypertension contained 33 men and 15 women; 25 men (76

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percent) and 8 women (53 percent) were smokers compared with 44 percent and 30 percent, respectively, of a group of 44 men and 44 women with nonmalignant hypertension. The difference is significant for men but does not reach significance for women.

VENOUS THROMBOSIS

The section of the 1979 Surgeon General's Report dealing with venous thrombosis noted a case control study by Vessey and Doll of 84 women who had venous thromboembolism (45). There was no significant relationship to smoking, although there was a trend (p =0.08) reasonably attributable to chance (46). Similarly, Lawson, Davidson, and Jick reported no association with smoking among 60 premenopausal women who used oral contraceptives and who had uncomplicated venous thromboembolism (22).

The issue is reopened, however, by a recent paper derived from the Walnut Creek Contraceptive Drug Study. The authors analyzed 38 cases of venous thromboembolic events among the approximately 16,700 women followed in the study. These women were matched with 8,174 controls from the same cohort, providing each case with 61 to 559 comparison subjects. The relative risk of cigarette smoking was 2.6 with a one-sided p value of less than 0.01. On multivariate analysis, the smoking effect was independent and remained significant. Of the 17 idiopathic cases of thromboembolic disease, 65 percent occurred in smokers, while 33 percent of the controls were smokers. The relative risk for smokers was 4.2. Both smoking and oral contraceptive use were independent risk factors for venous thromboembolic disease in this cohort of women (32).

The same section of the 1979 Surgeon General's Report noted a controversy about whether smokers who suffered myocardial infarction had a relative protective effect from leg vein thrombosis in the immediate post infarction period (45). The authors did not provide an analysis for each sex.

A recent investigation of women undergoing gynecologic operations has studied the incidence of deep vein thrombosis of the leg in relation to smoking. In the prospective study of 231 women, their smoking habits during the month before the operation were determined. The occurrence of deep vein thrombosis (DVT) was assessed by the radioactive fibrinogen technique, with routine scans on the first, third, and sixth postoperative days. Of the 231 patients, 99 smoked and 132 did not smoke. Eight of the smokers (8.1 percent) and 29 of the nonsmokers (22 percent) developed DVT. Following an analysis of other factors, the authors concluded that smoking provided an apparent "pro-

tective" effect against postoperative DVT, based on the fact that smokers constituted only 21 percent of the patients with DVT. They also noted that the women who developed DVT weighed more than those who did not and that smokers who developed CVT were more overweight than nonsmokers with DVT (5).

In a continuing prospective study of the relationship of blood clotting and blood thrombogenic properties to ischemic heart disease, Meade and associates have reported on a number of blood coagulation variables and their relationship to smoking among 1,426 men and 638 women in England (26). Forty-three percent of the men and 36 percent of the women were smokers. Smoking was not found to have an effect in women on factors V or VII, fibrinogen, fibrinolytic activity, antithrombin III, platelet adhesiveness, or platelet count. Smoking decreased fibrinolytic activity in men and decreased factor VIII activity in both men and women. Oral contraceptive users were found to show an increase in fibrinolytic activity only if the women were nonsmokers.

HIGH-DENSITY LIPOPROTEIN

High-density lipoprotein (HDL) is a protein complex that transports cholesterol in the blood. A higher level of HDL is correlated with a reduced risk of heart attack. It has been observed that women who smoke have lower levels of HDL than expected (1,4,9).

Oral Contraceptive Use, Smoking, and Cardiovascular Disease

The association of oral contraceptive use and an increased incidence of certain cardiovascular disorders has attracted much interest. Smoking has emerged as a strong synergistic risk factor, and an additional study has focused on smoking as an independent risk factor.

The effects of smoking and of estrogen and progestin contraceptives on the level of high-density lipoprotein in women have been studied by Bradley and associates. They measured serum HDL among almost 5,000 women between the ages of 21 and 62 (4). They reported that the use of oral estrogens raised the level of HDL significantly above the level in nonusers while progestin use lowered it. Combination drugs tended to change the HDL level according to their relative estrogen-progestin formulation. The average HDL concentration was reduced by smoking. Among nonsmoking women the HDL concentration was 63.7 ± 16.8 mg/dl. This was reduced by 2.2 mg/dl for those smoking half a pack per day; and by 7.3 mg/dl for those smoking

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one or more packs per day. A reduction in the HDL level among women who smoked was also reported from Holland. This study found an independent negative association with the HDL level among oral contraceptive users (1).

It has been reported from long-term studies that women using oral contraception have a two to threefold statistically significant increase in risk of venous thromboembolic disease when compared to those using other forms of contraception (47). This study concluded that smoking did not significantly increase the incidence of venous thromboembolism (46). By contrast, the Walnut Creek Study reported that smoking contributed to venous thromboembolism among both users and nonusers of oral contraceptives (32). Conclusions about the effect of smoking on venous thromboembolic phenomena, therefore, must be regarded as uncertain at this time since there are few relevant studies and they provide somewhat contrary conclusions.

In 1973, the Collaborative Group for the Study of Stroke in Young Women estimated that the relative risk of cerebral ischemia or thrombosis was approximately nine times greater for women who use oral contraceptives than for those who do not. A detailed analysis of smoking was not presented, but one of the study's striking findings was the high proportion of women with stroke who currently or at some time smoked cigarettes regularly (73.8 percent), compared with smoking rates of 43.4 percent among neighborhood controls aged 17 to 44. The study also found an increase in hemorrhagic strokes among white women. Almost half of the hemorrhagic strokes were attributable to bleeding from congenital aneurysms leading to subarachnoid hemorrhage (5). Recently an association between smoking and aneurysmal subarachnoid hemorrhage in both men and women has been documented (2).

The Walnut Creek Contraceptive Drug Study reported that in a cohort of approximately 16,700 women, the risk of subarachnoid hemorrhage for smokers was 5.7 times that of nonsmokers; the risk for oral contraceptive users was 6.5 times that of nonusers; and the relative risk for women who used both cigarettes and oral contraceptives was 22 times as great. Past users of oral contraceptives also had an increase in relative risk, but an analysis of risk was not possible because of the small number of cases (31).

The risk of myocardial infarction in women is increased by cigarette smoking and by the use of oral contraceptives; it is compounded when both are used together. For example, Mann and associates reported a retrospective study of 63 women below the age of 45 with acute myocardial infarction. The pro-

portion of heart attack patients who had used oral contraceptives in the previous months was significantly higher than expected. The relative risk for myocardial infarction among women smoking 25 or more cigarettes per day was 11.3 times greater than that among nonsmokers. Moreover, there was evidence for synergism of the two risks (23).

Jick, et al. reported a case control study of 107 women under age 46 who were discharged from the hospital after suffering nonfatal, acute myocardial infarctions (15,16,17). The annual risk of nonfatal myocardial infarction (MI) among healthy women aged 39 to 45 who both smoked and used estrogens for noncontraceptive purposes was approximately 1 in 750. They noted that although an acute myocardial infarction is uncommon in healthy young women, the risk appears to be substantial in women over the age of 38 who both use estrogens and smoke cigarettes (17).

In this same study, a relative risk of 14 was reported for oral contraceptive users compared with nonusers (90 percent confidence limits of relative risk from 5.5 to 37) (16). In women smoking more than 25 cigarettes per day the relative risk rose to 34 times that of women who were both nonusers and nonsmokers. While the number of subjects was small, the authors calculated that for women exposed to either oral contraceptives or smoking, but not both, the annual age-specific risks for nonfatal MI were roughly 1 per 190,000 at ages 27 to 37; 1 per 47,000 at ages 38 to 40; 1 per 23,000 at ages 40 to 43; and 1 per 16,000 at ages 44 and 45. If, however, both cigarettes and oral contraceptives are used, the annual age-specific risk is estimated to be much higher and the respective risks become 1 in 8,400; 1 in 920, 1 in 540, and 1 in 250. The authors report that a dose-response relationship exists between smoking and risk among their population of female myocardial infarction patients, such that smoking 1 to 14 cigarettes per day carried a relative risk of nonfatal myocardial infarction of 9.2; 15 to 25 cigarettes of 7.9; and 26 or more cigarettes of 21, relative to those who never smoked (15).

In another recent study of 234 pre-menopausal women who had suffered a first myocardial infarction and 1,742 control patients drawn from the hospital population, Shapiro and his co-workers found an association between recent oral contraceptive use and smoking (35). They found no evidence that past use of oral contraceptives was related to heart attack or that heightened risk was associated with increased duration of use of the oral contraceptives. For nonsmokers who used oral contraceptives, the rate of myocardial infarction increased fourfold compared to nonusers and nonsmokers; in those women who smoked 25 or more cigarettes a day but did not use oral con-

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