



Likelihood That a Woman Will Have No Major Risk Factors At the Time of First Myocardial Infarction or Stroke

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This article describes an analysis of data from a case-control study of myocardial infarction (MI) and ischemic stroke in women aged 45-74 years who had been inpatients at any of 10 Kaiser Permanente Northern California (KPNC) facilities from November 1991 to November 1994. Information on major risk factors for ischemic stroke (ie, diabetes, hypertension, and smoking) and MI (ie, diabetes, hypertension, smoking, and hypercholesterolemia) known at the time of the MI event was obtained at patient interviews. The percentage of patients and controls who had MI or stroke and one, two, three, or (for MI) four major risk factors was calculated along with the odds ratio and 95% confidence intervals for stroke according to the number of major risk factors.

In 25.8% of women with incident ischemic stroke and 17.5% of women with incident MI, no major risk factors for the disease were identified at time of hospital admission. Among women with incident stroke, absence of major risk factors was associated with younger age; among women with MI, absence of major risk factors was associated with older age, although the changes with age were not statistically significant in this group. Among women who had only one of these major risk factors at presentation, hypertension was seen significantly more often with increasing age, whereas among women who had stroke or MI, smoking was the risk factor seen significantly less often with increasing age.

The data show that a substantial minority of female patients with incident stroke and MI have no identified major risk factors at the time of their MI event.

Introduction

Epidemiologic research over the last three decades has elucidated a number of important risk factors for myocardial infarction (MI) and stroke. That hypertension, diabetes, and cigarette smoking increase the risk of both MI and ischemic stroke is now well established.^{1,2} These factors are associated with an increased risk for MI and stroke in women as well as in men.³ High levels of total serum cholesterol are an established risk factor for MI in both men and women,¹ but the question of whether high cholesterol increases the risk for stroke remains controversial.²

For persons with MI and stroke, recognition and identification of risk factors is an important part of clinical care because postevent efforts to prevent recurrent disease are increasingly focused on management of these risk factors. The presence or absence of risk factors can influence physicians' assessment of disease probability as well as their decisions about diagnostic testing in people who present with symptoms of MI or stroke. A 40-year-old woman with vague chest pain who also smokes, has hypertension, and serum cholesterol level of 300 mg/dL is more likely to have coronary disease than a normotensive nonsmoker with a cholesterol level of 180 mg/dL who has the same kind of chest pain. Given the probability of coronary artery disease, treadmill testing is a reasonable diagnostic choice in the

woman with risk factors but may be reasonably foregone in the woman without risk factors.

Largely absent from the literature on cardiovascular epidemiology is information on the likelihood that a person will not have any risk factors when they are first seen with cardiovascular disease. Information about cardiovascular disease and risk factors in women is particularly sparse, because women have not been the subject of intensive epidemiologic investigation until recently. The present analysis of data from a previously completed study was done to answer the question: What is the likelihood that women with a confirmed diagnosis of MI or stroke have no identified major risk factors when they present with the condition?

Methods

Case Ascertainment and Classification

The methods used for case ascertainment and classification have been described in detail elsewhere.^{4,5} Briefly, an attempt was made to identify all fatal and nonfatal strokes and MIs in women aged 45-74 years who had been inpatients in any of 10 medical centers of Kaiser Permanente Northern California (KPNC) from November 1991 to November 1994. Sources for case ascertainment included hospital admission and discharge records, emergency department logs, and payments for out-of-plan hospitalizations.

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Hypertension, diabetes, and current smoking were considered major risk factors for ischemic stroke. These three factors plus hypercholesterolemia were considered major risk factors for MI.

Stroke was defined as the new onset of rapidly developing symptoms and signs of loss of cerebral function with no apparent cause other than that of vascular origin. Patients who had a history of cerebrovascular disease were excluded. Details of our protocol for verifying the diagnosis of stroke and for subclassifying stroke by type appear in our prior publication.⁵ The present analysis includes only stroke classified as ischemic.

Diagnostic criteria for myocardial infarction were adapted from those of the American Heart Association Council on Epidemiology.⁶ These criteria use presence or absence of chest pain, results of cardiac enzyme measurement, and electrocardiograms to classify events as definite, probable, or suspect MI or not MI. Consistent with other epidemiologic studies of MI based on these criteria, we included events categorized as definite or probable MI.

For each patient, an attempt was made to interview one control, matched by year of birth as well as medical facility at which care was usually received. To obtain one interviewed control per case, three potential con-

trols were selected at random from among all female members of the Kaiser Permanente Medical Care Program. If the first potential control could not be located, declined to participate, or spoke a language other than English or Spanish, an attempt was made to enroll the second potential control and, if necessary, the third.

Information Sources

Eligible patients and controls were interviewed in person by trained interviewers using a standardized instrument. If a study subject had died or was unable to communicate verbally, an attempt was made to interview a proxy. Interview questions pertained to an index date, which was the date of symptom onset for each case and matched control.

Hypertension, diabetes, and current smoking were considered major risk factors for ischemic stroke. These three factors plus hypercholesterolemia were considered major risk factors for MI.

Family history was not considered as a major risk factor because it is not generally described as a ma-

Table 1. Number and percentage distribution of major risk factors for myocardial infarction^a and ischemic stroke^b in patients and controls and age-adjusted odds ratios by number of risk factors

No. of major risk factors	Myocardial infarction			Ischemic stroke		
	Number (%)		Age-adjusted odds ratio (95% CI)	Number (%)		Age-adjusted odds ratio (95% CI)
	Patients	Controls		Patients	Controls	
0	93 (17.5)	269 (49.4)	1.0 (referent)	105 (25.8)	240 (56.9)	1.0 (referent)
1	225 (42.3)	197 (36.1)	3.3 (2.4, 4.5)	185 (45.5)	145 (34.4)	3.0 (2.2, 4.1)
HBP only	69 (13.0)	71 (13.0)	2.6 (1.7, 3.9)	97 (23.8)	84 (19.9)	2.7 (1.8, 3.9)
DM only	37 (7.0)	14 (2.6)	7.2 (3.7, 14.0)	29 (6.9)	12 (2.8)	5.5 (2.7, 11.3)
Smoking only	75 (14.1)	54 (9.9)	4.3 (2.8, 6.7)	59 (14.5)	49 (11.6)	2.8 (1.8, 4.3)
High cholesterol only	44 (8.3)	58 (10.6)	2.1 (1.3, 3.3)	--	--	--
2	171 (32.1)	73 (13.4)	6.8 (4.7, 9.7)	111 (27.3)	35 (8.3)	7.4 (4.7, 11.5)
3	37 (7.0)	6 (1.1)	17.9 (7.3, 43.8)	6 (1.5)	2 (0.5)	6.7 (1.3, 33.8)
4	6 (1.1)	0 (0.0)	Inestimable	--	--	--
All	532	545		407	422	

^aMajor risk factors for myocardial infarction are hypertension, diabetes, smoking, and high cholesterol level.

^bMajor risk factors for ischemic stroke are hypertension, diabetes, and smoking.

Note: Due to rounding, percentages do not total 100.0.



major risk factor, and because no standard definition of positive family history exists for either stroke or MI. Other risk factors for MI, stroke, or both (eg, homocysteinemia and fibrinogen levels, markers of response to chronic inflammation) were not assessed and could not be examined as risk factors.

Hypertension was defined as a "yes" to a question about use of medication for high blood pressure. Diabetes was defined as a "yes" to a question asking about use of insulin or pills for diabetes. Women who stated that they had been told by a physician that they had a high cholesterol level were classified as having hypercholesterolemia. We did not use measured levels of cholesterol, because data were missing for a large percentage of subjects. A study subject was defined as a nonsmoker if she answered "no" to the question, "Have you ever smoked cigarettes?"; if she answered "yes" to this question, she was categorized as a current regular smoker on the basis of her answer to the question, "On [index date], were you still smoking regularly?" (Regularly means at least five cigarettes per week, almost every week.) On the basis of this information, study subjects were classified as having one, two, three, or (for MI) four major risk factors.

Analysis

The exposure odds ratio was used to estimate relative risk of ischemic stroke and MI in women with one, two, three, or (for MI) four major risk factors. Odds ratios for stroke and MI were estimated separately for each major risk factor among women with only one risk factor. The percentage of patients with one, two, three, or (for MI) four major risk factors was also calculated by age in three categories (age 45-54 years, age 55-64 years, age 65-74 years). The statistical significance of changes in the percentage of cases with no major risk factors by age was examined using the chi-square statistic. A probability value less than 0.05 was considered statistically significant.

Results

Of 758 women who had confirmed diagnoses of ischemic stroke, 407 patients and 422 controls remained for analysis after we excluded women on the basis of patient or physician refusal, proxy interviews, and self-reported history of cerebrovascular disease at time of interview. Of 685 women who had confirmed diagnoses of definite or probable MI, 532 patients and 545 controls remained for the analysis after we excluded women on the basis of patient or physician refusal, proxy interview, and self-reported coronary heart disease at time of interview.

Table 1 shows the distribution of ischemic stroke and MI among patients and controls according to number of major risk factors along with age-adjusted odds ratios for stroke and MI in women who had one, two, three, or (for MI) four major risk factors. Also shown are the age-adjusted odds ratios for ischemic stroke and MI in women with only one major risk factor according to the risk factor. The odds ratios for both stroke and MI increased according to the number of major risk factors. For women with one major risk factor, odds ratios were highest in women with diabetes for both ischemic stroke and MI, although the 95% confidence limits for these estimates overlapped.

Among women with stroke, 25.8% had no major risk factors identified at the time of the incident event. Among women with MI, 17.5% had no major identified risk factors.

Table 2 shows the percentage distribution of major risk factors for ischemic stroke by age for patients only. The percentage of patients with incident stroke who had no major risk factors decreased with age, but the change with age was not statistically significant (p = 0.08).

Table 3 shows the percentage distribution of major risk factors for MI by age for patients only. The percentage of patients with incident MI who had no major risk factors increased with age, but the change with age was not statistically significant (p = 0.15).

Among women with stroke, 25.8% had no major risk factors identified at the time of the incident event. Among women with MI, 17.5% had no major identified risk factors.

Table 2. Number and percentage distribution of major risk factors^a for ischemic stroke in women with incident ischemic stroke by age at event

No. of major risk factors	No. (%) of women		
	Age 45-54 yr	Age 55-64 yr	Age 65-74 yr
0	24 (35.8)	29 (21.0)	52 (25.7)
1	26 (38.8)	65 (47.1)	94 (46.5)
HBP only	8 (11.9)	29 (21.0)	60 (29.7)
DM only	6 (9.0)	9 (6.5)	14 (6.9)
Smoking only	12 (17.9)	27 (19.6)	20 (9.9)
2	14 (20.9)	42 (30.4)	55 (27.2)
3	3 (4.5)	2 (1.4)	1 (0.5)
Total	67	138	202

^a Major risk factors for ischemic stroke are hypertension, diabetes, and smoking.

Note: Due to rounding, percentages do not total 100.0.

Knowing about the epidemiologic associations between major risk factors and disease may lead physicians to expect that women with disease will have major risk factors, although we have no proof of this speculation.

Among patients with only one risk factor, the percentage of patients with only hypertension increased significantly with age for patients with stroke ($p < 0.01$) and for patients with MI ($p < 0.01$); the percentage of patients whose only risk factor was smoking decreased significantly with age ($p < 0.05$).

Discussion

Epidemiologic research has identified several major risk factors for ischemic stroke and MI in women. Our analysis of data from a large case-control study in women confirms that the risk of both MI and stroke is substantially higher in women with these well-recognized major risk factors, whether alone or in combination. Knowledge of the relation between these factors and disease is important for designing programs aimed at preventing the diseases.

Clinicians see patients—not cases and controls. Knowing about the epidemiologic associations between major risk factors and disease may lead physicians to expect that women with disease will have major risk factors, although we have no proof of this speculation. Our data show that a substantial minority of female patients with incident stroke and MI

have no major risk factors identified at the time of their event.

The pattern of risk factors among women with only one major risk factor is also of interest. For women who had MI or stroke, cigarette smoking decreased with increasing age as a single risk factor, whereas hypertension increased with increasing age as a single risk factor in these women.

Unfortunately, we have no comparable data about men. Similar analyses of risk factors with incident disease could not be identified for either men or women. Information on major risk factors was derived from self-report, and the study results should be interpreted recognizing this limitation. More important, the absence of identified major risk factors does not mean that the woman had no risk factors; occurrence of a clinical event may prompt clinical testing that leads to a previously unrecognized diagnosis of hypertension, diabetes, or hypercholesterolemia. Thus, the present analysis should not be interpreted to mean that no major risk factors were present at the time of the incident event, only that no major risk factors had been identified at that time. An increase in rate of screening for dyslipidemia and/or hypertension might change these percentages. Finally, some risk factors were not considered here. These risk factors include family history of heart disease or stroke; obesity; dyslipidemias other than hypercholesterolemia; hyperhomocysteinemia; and others.

This study found that the absence of identified major risk factors is not uncommon in women patients with incident stroke and MI. Among patients with only one identified major risk factor, the pattern of major risk factors changed with age. ❖

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Table 3. Distribution of major risk factors^a for myocardial infarction among women with incident myocardial infarction by age at event

No. of major risk factors	No. (%) of women		
	Age 45-54 yr	Age 55-64 yr	Age 65-74 yr
0	16 (13.1)	29 (16.0)	48 (21.0)
1	48 (39.3)	74 (40.9)	103 (45.0)
HBP only	9 (7.4)	18 (9.9)	42 (18.3)
DM only	7 (5.7)	11 (6.1)	19 (8.3)
Smoking only	28 (23.0)	29 (16.0)	18 (7.9)
High cholesterol only	4 (3.3)	16 (8.8)	24 (10.5)
2	43 (35.2)	65 (35.9)	63 (27.5)
3	11 (9.0)	13 (7.2)	13 (5.7)
4	4 (3.3)	0 (0.0)	2 (0.9)
Total	122	181	229

^a Major risk factors for ischemic stroke are hypertension, diabetes, smoking, and high cholesterol level.
Note: Due to rounding, percentages do not total 100.0.