Prospective Study of Aspirin Use and Risk of Stroke in Women

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Background and Purpose—In secondary prevention, aspirin reduces risk of ischemic stroke. In primary prevention of stroke, however, the role of aspirin is uncertain, especially in women.

Methods—In 1980, 79 319 women in the Nurses' Health Study cohort, 34 to 59 years of age and free of diagnosed cardiovascular disease, cancer, and rheumatoid arthritis, completed questionnaires that included information on aspirin use. Data on aspirin use were updated in 1982, 1984, and 1988. By 1994, after 994 231 person-years of follow-up, 503 incident strokes (295 ischemic strokes, 100 subarachnoid hemorrhages, 52 intraparenchymal hemorrhages, and 56 strokes of undetermined type) were documented.

Results—There was no clear relationship between aspirin use and risk of total stroke; risk was slightly reduced among women who took 1 to 6 aspirin per week and slightly increased among women who took 7 or more aspirin per week. Women who took 1 to 6 aspirin per week had a lower risk of large-artery occlusive infarction compared with women who reported no aspirin use; after simultaneous adjustment for other cardiovascular risk factors and selected nutrients, the multivariate relative risk was 0.50 (95% CI 0.29 to 0.85, $P=0.01$). Women who took 15 or more aspirin per week had an excess risk of subarachnoid hemorrhage; the multivariate relative risk was 2.02 (95% CI 1.04 to 3.91, P for trend$=0.02$). The reduction in large-artery occlusive infarction with aspirin was of greater magnitude for older, hypertensive, or smoking women than for younger, nonhypertensive, or nonsmoking women; the elevation in subarachnoid hemorrhage with aspirin was also more apparent for older or hypertensive women than for younger or nonhypertensive women. Aspirin use was not associated with risk of other subtypes of stroke.

Conclusions—These prospective data indicate that women who take 1 to 6 aspirin per week have a reduced risk of large-artery occlusive infarction, but those who use 15 or more aspirin per week have an increased risk of subarachnoid hemorrhage. This observational study suggests benefits of aspirin for ischemic stroke with low frequency of use and hazards for hemorrhagic stroke with high frequency of use, particularly among older or hypertensive women. Thus, the effect on total stroke will depend on the dose of aspirin and the distribution of stroke subtypes and risk factors in the population. **(*Stroke*. 1999;30:1764-1771.)**

Key Words: aspirin ■ prevention, primary ■ stroke ■ stroke classification

Randomized clinical trials have demonstrated a benefit of aspirin in the secondary prevention of ischemic stroke in both men and women.[1] For primary prevention, the evidence is less certain. Two previous trials in men were inconclusive, perhaps because of the small numbers of strokes.[2,3] These trials, however, suggested possible excess risks of disabling stroke[2] or hemorrhagic stroke[3] in the aspirin group. Aspirin inhibits platelet aggregation,[4–7] which may reduce risk of ischemic stroke[1] but may raise risk of hemorrhagic stroke.[3]

In observational data, 1 prospective study of elderly men and women showed no significant association between aspirin use and risk of stroke: compared with aspirin nonusers, the age-adjusted relative risks (RRs) of total stroke were 0.87 to 0.88 for nondaily aspirin users and 1.22 to 1.27 for daily users.[8] In that study, data were limited to nondaily or daily use of aspirin, with adjustment only for age and sex. In a previous report based on 6 years' prospective data from the Nurses' Health Study,[9] we found no significant relation between aspirin use and risk of total stroke, ischemic stroke, or hemorrhagic stroke. The multivariate RR of total stroke was 0.99 (95% CI 0.71 to 1.36, $P=0.94$) for women who took 1 to 6 aspirin per week compared with women who took no aspirin, but the number of strokes was relatively small (total, n=198). After 14 years' follow-up, the Nurses' Health Study had 2.5 times the number of strokes (n=503), which allowed us to investigate in greater detail the relation of aspirin use to stroke as well as stroke subtypes.

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***Stroke* is available at http://www.strokeaha.org**

Subjects and Methods

Population

The Nurses' Health Study began in 1976, when 121 700 female registered nurses (98% white) completed questionnaires with items about lifestyle and medical history, including previous cardiovascular disease, cancer, diabetes, hypertension, and high serum cholesterol concentration.[10] Every 2 years, follow-up questionnaires have been sent so that information could be updated and newly diagnosed major illnesses identified. The present investigation was restricted to the women who responded to the 1980 questionnaire, which was the first to include questions about aspirin use, and who were free of cancer (except nonmelanoma skin cancer), myocardial infarction, angina, coronary revascularization, stroke, other cardiovascular diseases, and rheumatoid arthritis in 1980. Women who reported regular use of nonsteroidal anti-inflammatory analgesics other than aspirin (n=3965) were also excluded; 79 319 women aged 34 to 59 years remained for analysis.

Aspirin Use

Data on regular aspirin use were obtained in 1980, 1982, 1984, and 1988. In 1980, the participants were asked if they currently used aspirin during most weeks; if so, they were to record the number of aspirin tablets or capsules taken per week. In 1982, the participants were asked if they currently used aspirin at least once per week, and if so, how many aspirin they took per week. The 1984 and 1988 questionnaires inquired about the average number of days each month that aspirin was taken, and the number of aspirin usually taken on those days; from these questions we calculated the average number per week. We did not ask about dose, and assumed that each contained 325 mg. This assumption is reasonable, because until very recently most women took the adult form of aspirin (325 mg in the United States) and not baby aspirin. The information on aspirin use was updated for the analyses because regular aspirin use (1 or more per week) changed markedly during the follow-up (40% in 1980, 42% in 1982, 72% in 1984, and 65% in 1988). The change in aspirin use was primarily observed in the category of 1 to 2 aspirin per week: 14% in 1980, 17% in 1982, 36% in 1984, and 32% in 1988. Aspirin use in 1990 and 1992 was ascertained by the question, "How many days each month do you take aspirin? None, 1 to 4, 5 to 14, 15 to 21, 22 or more," but the quantity of aspirin was not asked. Thus, we did not estimate the use of aspirin in the same way as we did in 1980, 1982, 1984, and 1988. However, the proportion of women who reported taking aspirin 1 to 4 days or more per month, which would be expected to be approximately equal to or greater than the proportion of women taking aspirin 1 or more tablets per week, was 54% in 1990 and 54% in 1992. Use of other types of analgesics such as acetaminophen was not asked until 1990.

The biennial questionnaires also elicited information about age, current weight, current and past cigarette smoking, menopausal status, use of postmenopausal hormones, and previous diagnoses of coronary heart disease, stroke, and other major illnesses. Data on alcohol intake were available in 1980 and updated in 1984, 1986, and 1990. The 1980 questionnaire also inquired about vigorous exercise and intake of multivitamins and vitamin E supplements. Height was ascertained in 1976. Information was available on selected nutrients potentially associated with risk of total stroke or stroke subtypes; ie, intake of saturated fat, animal protein, calcium, potassium, n-3 polyunsaturated fatty acids (eicosapentaenoic and docosahexaenoic acids), and dietary vitamin C. Intake of these nutrients was estimated with use of the 1980 semiquantitative food frequency questionnaire.[11] Nutrient intakes were adjusted for total energy intake by the residual approach.[12]

Ascertainment of Stroke

Strokes were included in the analyses if they occurred after the date of return of the 1980 questionnaire but before June 1, 1994. Women who reported a nonfatal stroke on a follow-up questionnaire were asked for permission to review their medical records. Nonfatal strokes for which confirmatory information was obtained by telephone interview or letter, but for which no medical records were obtainable, were regarded as probable (62 of 416 nonfatal strokes [14.9%]). Fatal strokes were initially ascertained by reports of relatives or postal authorities and a search of the National Death Index[13] and documented by medical records and death certificates. Mortality follow-up was >98% complete.[13] Fatal strokes for which confirmatory information was obtained by telephone interview, letter, or death certificate, but for which no medical records were obtainable, were regarded as probable (13 of 87 fatal strokes [14.9%]). Medical records were reviewed by physicians blinded to the data on aspirin use and other risk factors. Only confirmed and probable strokes were included in the analyses for all strokes. For analyses of specific stroke subtypes, only confirmed cases were included.

Strokes were confirmed by medical records according to the criteria of the National Survey of Stroke,[14] which requires a constellation of neurological deficits, sudden or rapid onset, lasting ≥24 hours, or until death; events were further subclassified as subarachnoid hemorrhage, intraparenchymal hemorrhage, ischemic stroke (thrombotic or embolic), or stroke of unknown cause. Subarachnoid hemorrhage was defined as hemorrhage in the subarachnoid space. Intraparenchymal hemorrhage was defined as hemorrhage in intraparenchymal regions of the brain not due to an aneurysm or arteriovenous malformation. Ischemic stroke was cerebral infarction caused by in situ thrombi (thrombotic stroke) or by emboli from extracranial sources (embolic stroke). Infarction was considered if evidence of embolic sources was present in the medical record and if imaging studies indicated hemorrhagic infarction and other clinical details from neurology consult supported the diagnosis. Sources of emboli included ulcerating atherosclerotic plaque in the carotid artery, mural thrombi associated with myocardial infarction, a consequence of surgery for coronary heart disease, nonvalvular atrial fibrillation, valvular heart disease, bacterial endocarditis, cardiomyopathy, and other sources. For each subtype of stroke, definite diagnosis was made when CT scan, MRI, angiography, surgery, or autopsy confirmed the lesion; otherwise probable diagnosis was made. The proportion of strokes with CT or MRI confirmation among those with available medical records was 89%.

Thrombotic strokes were further classified as large-artery occlusive infarction, lacunar infarction, or unclassified thrombotic infarction on the basis of the results of CT scan, MRI, or autopsy, according to the criteria of Perth Community Stroke Study.[15] Large-artery occlusive infarction was defined as infarction involving the cortical artery regions in the cerebrum and cerebellum, presumably caused by in situ thrombosis of large- or medium-sized cerebral arteries. Definite diagnosis was made when CT scan, MRI, or autopsy showed confirmatory findings. If imaging studies showed negative findings but the patient had had cortical signs, a diagnosis of probable large-artery occlusive infarction was made. Lacunar infarction was defined as infarction of a focal, small, and deep area, such as internal capsule, corona radiata, basal ganglia, or brain stem, without involvement of cortex, which is caused by occlusion of small penetrating arteries. Definite diagnosis was made when CT scan, MRI, or autopsy showed confirmatory findings. If imaging studies were negative but the patient had a lacunar syndrome (pure motor stroke, pure sensory stroke, ataxic hemiparesis, dysarthria–clumsy hand syndrome, or sensorimotor stroke), a diagnosis of probable lacunar infarction was made. Other thrombotic stokes were regarded as unclassified thrombotic infarction. We combined the data for definite and probable cases because they provided similar results (n=66 and n=16 for definite and probable large-artery occlusive infarction, and n=75 and n=65 for definite and probable lacunar infarction, respectively).

Statistical Analyses

The present analyses were based on incidence rates of stroke during 14 years of follow-up from 1980 to 1994. The participants were classified into the 5 groups of aspirin use as reported on the 1980, 1982, 1984, and 1988 questionnaires: 0, 1 to 2, 3 to 6, 7 to 14, or ≥15 aspirin per week. For the first 2 years of follow-up, person-months of follow-up for each woman were allocated according to the 1980 exposure variables, and subsequent follow-up was based on the

TABLE 1. Distribution of Potential Risk Factors in a Cohort of 67 787 Women in 1984, According to Aspirin Use

	Aspirin per Week, n				
	0	1–2	3–6	7–14	≥15
Women, n	19 233	24 702	11 258	7900	4694
Mean age, y	50.3	49.8	49.4	50.9	51.8
Women with potential risk indicators, %*					
Current smoking	25.6	23.2	23.1	23.6	26.2
Hypertension	19.5	18.5	21.2	24.9	29.1
Diabetes	3.3	2.5	2.5	3.0	3.5
High cholesterol levels	8.1	7.2	7.6	8.8	9.4
Current hormone use in postmenopausal women	18.0	18.5	20.7	22.8	20.9
Body mass index ≥29 kg/m^2	16.0	14.1	16.7	18.3	24.8
Vigorous exercise†	44.7	45.8	45.5	44.6	42.3
Alcohol intake ≥25 g/d	7.7	7.3	7.7	8.9	8.1
Multivitamin use	33.5	35.2	38.5	42.3	43.5
Vitamin E use	15.8	15.8	17.8	19.1	19.9
Highest quintile of nutrients					
Saturated fat	20.0	19.4	20.3	20.1	21.8
n-3 polyunsaturated fatty acids	20.2	19.0	19.8	19.6	20.1
Animal protein	19.9	18.7	19.8	19.8	22.9
Calcium	20.8	20.0	21.9	23.1	27.7
Dietary vitamin C	20.4	18.8	17.7	19.5	19.3

*Age-adjusted by the 5-year age categories of the age distribution of the cohort.
†Sweat-producing exercise at least once a week.

updated aspirin use information. Exposure status for age, current weight, smoking status, menopausal status, use of postmenopausal hormones, use of multivitamins and vitamin E supplements, and histories of hypertension, diabetes, and high serum total cholesterol levels were updated according to information on biennial follow-up questionnaires until death or an end point (stroke) was reached, or until May 31, 1994.

The RR of stroke was defined as the incidence rate of stroke for women in each aspirin category, divided by the corresponding rate for the women in the reference category (no aspirin). RRs with 95% CIs were adjusted for age in 5-year categories. We conducted tests for linear trend across the aspirin-use categories using mean number of aspirin tables in each category. To adjust simultaneously for other cardiovascular risk factors, we used pooled logistic regression over the seven 2-year intervals.[16] Categories for covariates in multivariate analyses are indicated in footnotes to the tables. We also conducted stratified analyses by age (34 to 54 and ≥55 years), a history of hypertension (no and yes), and smoking status (nonsmokers and current smokers) to examine modification of the association between aspirin use and risk of stroke. In these subanalyses, tests for linear trend across the aspirin-use categories were unreliable in some strata due to the small number of cases, but test results were presented for reference.

Results

There were no strong relationships between aspirin use and the prevalence of coronary risk factors in 1984, a year approximately at the midpoint of the follow-up period (Table 1). Seventy-two percent of the participants reported taking aspirin regularly, with a half of them taking 1 to 2 aspirin per week. Women who took aspirin were slightly more likely to take postmenopausal hormones and vitamin supplements and to have a higher intake of calcium than those who took no aspirin. Women who took ≥15 aspirin per week also had a higher prevalence of hypertension, high cholesterol levels, and overweight, and were less physically active than women in the other aspirin categories. Women who took 1 to 6 aspirin per week had a lower prevalence of diabetes and a lower frequency of reported high cholesterol levels.

During 944 231 person-years of follow-up from 1980 to 1994, we documented 503 incident cases of stroke. Of the strokes, 295 were ischemic strokes, 100 were subarachnoid hemorrhages, 52 were intraparenchymal hemorrhages, and 56 were strokes of undetermined type. Ischemic strokes consisted of 33 embolic infarctions, 82 large-artery occlusive infarctions, 140 lacunar infarctions, and 40 thrombotic infarctions of undetermined type. The carotid artery was examined by either ultrasonography or angiography to exclude the possibility of embolic infarction for all large-artery occlusive infarctions except for 1 probable case.

There was no clear relationship between aspirin use and risk of total stroke; a slight risk reduction was observed among women who took 1 to 6 aspirin per week, and a slight risk increase was seen among women who took ≥7 aspirin per week (Table 2). Women who took 1 to 2 aspirin per week and those who took 3 to 6 aspirin per week showed a lower risk of large-artery occlusive infarction than women who took no aspirin, after simultaneous adjustment for other cardiovascular risk factors as well as selected nutrients; multivariate RR was 0.50 (95% CI 0.29 to 0.85, $P=0.01$) for 1 to 6 aspirin per week. The results were similar when we restricted the analyses to definite cases (n=66); the respec-

TABLE 2. Relative Risk (95% CI) of Stroke Subtypes in a Cohort of 79 319 Women From 1980 to 1994, According to Aspirin Use

	Aspirin per Week, n					
	0	1–2	3–6	7–14	≥15	*P* for Trend
Person-years	387 138	263 428	137 649	102 659	53 304	
All stroke						
Cases	201	114	60	87	41	
Age-adjusted RR*	1.0	0.74 (0.59–0.93)	0.80 (0.60–1.07)	1.33 (1.03–1.72)	1.25 (0.90–1.75)	0.005
Multivariate RR†	1.0	0.85 (0.67–1.08)	0.87 (0.65–1.16)	1.31 (1.01–1.69)	1.17 (0.83–1.64)	0.06
Ischemic stroke						
Cases	118	74	34	52	17	
Age-adjusted RR*	1.0	0.80 (0.60–1.07)	0.77 (0.53–1.13)	1.30 (0.93–1.80)	0.87 (0.52–1.43)	0.66
Multivariate RR†	1.0	0.92 (0.68–1.24)	0.83 (0.56–1.21)	1.22 (0.88–1.71)	0.79 (0.48–1.33)	0.79
Embolic infarction						
Cases	12	10	4	5	2	
Age-adjusted RR*	1.0	1.02 (0.44–2.36)	0.87 (0.28–2.69)	1.18 (0.43–3.26)	...	0.98
Multivariate RR†	1.0	1.17 (0.50–2.78)	0.93 (0.30–2.92)	1.19 (0.41–3.45)	...	0.99
Large-artery occlusive infarction						
Cases	41	15	7	15	4	
Age-adjusted RR*	1.0	0.47 (0.26–0.85)	0.46 (0.21–1.02)	1.09 (0.60–1.98)	0.60 (0.22–1.64)	0.86
Multivariate RR†	1.0	0.51 (0.28–0.93)	0.47 (0.21–1.06)	1.00 (0.55–1.82)	0.52 (0.19–1.47)	0.53
Lacunar infarction						
Cases	48	35	18	31	8	
Age-adjusted RR*	1.0	0.92 (0.59–1.43)	1.00 (0.58–1.72)	1.88 (1.18–2.97)	0.99 (0.47–2.08)	0.29
Multivariate RR†	1.0	1.04 (0.67–1.63)	1.07 (0.62–1.84)	1.76 (1.11–2.78)	0.91 (0.43–1.94)	0.58
Hemorrhagic stroke						
Cases	61	31	22	22	16	
Age-adjusted RR*	1.0	0.69 (0.45–1.07)	0.97 (0.60–1.58)	1.19 (0.73–1.95)	1.68 (0.96–2.92)	0.01
Multivariate RR†	1.0	0.76 (0.49–1.19)	1.04 (0.64–1.71)	1.25 (0.76–2.05)	1.63 (0.93–2.86)	0.02
Intraparenchymal hemorrhage						
Cases	24	8	7	9	4	
Age-adjusted RR*	1.0	0.43 (0.19–0.95)	0.78 (0.33–1.80)	1.10 (0.51–2.39)	0.98 (0.34–2.83)	0.52
Multivariate RR†	1.0	0.50 (0.22–1.14)	0.88 (0.38–2.06)	1.17 (0.54–2.56)	1.02 (0.35–2.98)	0.55
Subarachnoid hemorrhage						
Cases	37	23	15	13	12	
Age-adjusted RR*	1.0	0.87 (0.52–1.47)	1.11 (0.61–2.01)	1.26 (0.66–2.37)	2.20 (1.13–4.25)	0.006
Multivariate RR†	1.0	0.94 (0.55–1.61)	1.16 (0.63–2.13)	1.28 (0.67–2.43)	2.02 (1.04–3.91)	0.02

*Adjusted for age (5-year categories) and time interval.

†Also adjusted for smoking status (5 categories); body mass index (5 categories); alcohol intake (4 categories); menopausal status and postmenopausal hormone use; vigorous exercise (yes vs no); multivitamin use (yes vs no); vitamin E use (yes vs no); histories of hypertension, diabetes, and high cholesterol levels (yes vs no); and intake (quintile) of saturated fat, animal protein, calcium, n-3 polyunsaturated fatty acids, and dietary vitamin C.

tive RRs were 0.55 (95% CI 0.31 to 0.96, $P=0.02$) after age adjustment and 0.55 (95% CI 0.31 to 0.99, P for trend$=0.04$) after multivariate adjustment. This quantity of aspirin use was not associated with other subtypes of stroke. For lacunar infarction, an excess risk was observed among women who took 7 to 14 per aspirin per week but not among those with the highest aspirin intake. Women who took ≥15 aspirin per week had a 2-fold increase in risk of subarachnoid hemorrhage compared with women who took no aspirin; multivariate RR was 2.02 (95% CI 1.04 to 3.91, P for trend$=0.02$). When we restricted the analyses to definite cases (n$=87$), the respective RRs were 2.03 (95% CI 0.99 to 4.15, P for trend$=0.02$) after age adjustment and 1.76 (95% CI 0.86 to 3.62, P for trend$=0.06$) after multivariate adjustment, which were similar to, although somewhat weaker than, the relationship we observed when definite and probable cases were combined.

The overall risk reduction for large-artery occlusive infarction with use of 1 to 6 aspirin per week was similar among women aged 34 to 54 years and women aged 55 years or older, but the association was statistically significant only among women of older age groups (Table 3). The risk

reduction for large-artery occlusive infarction with aspirin use was more evident among hypertensive or smoking women than among nonhypertensive or nonsmoking women; the risk reduction was statistically significant only among hypertensive or smoking women.

The risk elevation for subarachnoid hemorrhage with aspirin use was more evident among older or hypertensive women than younger or nonhypertensive women; there was a 3-fold excess risk with use of ≥15 aspirin per week among older or hypertensive women (Table 3). The risk elevation for subarachnoid hemorrhage with aspirin use was similar among smoking and nonsmoking women.

Discussion

In this large prospective study, women who self-selected aspirin use had no material decreased or increased risk of total stroke after adjustment for various cardiovascular risk factors and selected nutrient variables. However, we found differential effects of aspirin use by stroke subtype; aspirin was associated with a reduced risk of large-artery occlusive infarction and an increased risk of subarachnoid hemorrhage. In these data, the benefit on occlusive infarction was evident among women taking 1 to 6 aspirin per week and a hazard for subarachnoid hemorrhage was observed only for those taking ≥15 aspirin per week. These associations with aspirin were more evident among the subgroups of older, hypertensive, and smoking women for large-artery occlusive infarction, and among older and hypertensive women for subarachnoid hemorrhage.

Risk reduction in large-artery occlusive infarction among women taking 1 to 6 aspirin per week is plausible because this type of stroke is primarily caused by in situ thrombosis in large- or medium-sized cerebral arteries. It thus has a pathophysiological[17–19] and risk factor profile[17–21] similar to that of coronary heart disease, for which a protective effect of low-dose aspirin use has been demonstrated.[3]

Aspirin irreversibly inhibits synthesis of thromboxane A_2 in platelets and cyclooxygenese-dependent aggregation of platelets.[22,23] A daily dose of aspirin required to inhibit platelet aggregation after 7 to 10 days is <80 mg[4–6] regardless of individual variation,[4,6] and the inhibitory effect of a single dose of aspirin (325 mg) lasts at least 3 days.[4] Thus, 1 aspirin at 3-day intervals (2 aspirin per week) is enough to achieve constant reduction of platelet aggregation. On the other hand, a single dose of aspirin substantially reduces synthesis of the strong vasodilator, prostacyclin (PGI_2), in vascular endothelial cells,[4,7] but its synthesis recovers completely within 1 day[4] (for bradykinin-stimulated PGI_2, within 6 hours[22]). Use of <1 aspirin per day is likely to avoid significant inhibition of prostacyclin synthesis. Although the clinical relevance of prostacyclin sparing has not been demonstrated, it is possible that low-dose aspirin use may conserve vasodilation while reducing platelet aggregation, thereby potentially maximizing risk reduction for large-artery occlusive infarction and myocardial infarction. According to in vivo human experiments, 3.5 mg/kg or 20 to 40 mg of aspirin every 2 or 3 days is most likely to inhibit platelet aggregation without significantly affecting prostacyclin production.[4,6] Two previous randomized controlled trials of aspirin in primary prevention of cardiovascular disease,[2,3] however, did not answer the question of whether 2 aspirin per week exert a clinically detectable antithrombotic effect, because they had small numbers of ischemic strokes and did not differentiate subtype of strokes.

A lack of reduced risk of embolic infarction with low-dose aspirin use is puzzling. However, this end point includes emboli of heterogeneous origins. Previous clinical trials suggest that aspirin is beneficial for the secondary prevention of embolic infarction among persons with carotid stenosis and myocardial infarction,[1] but the data are less clear for patients with atrial fibrillation.[23,24] In our study, none of the subclasses of embolic origin had enough cases to be analyzed separately (n=7 for ulcerative or complicated plaque in carotid arteries, n=5 for cardiac operation for coronary heart disease, n=11 for valvular heart disease, n=6 for nonvalvular atrial fibrillation, and n=4 for other causes).

We did not find any apparent benefits of aspirin on risk of lacunar infarction. In a secondary prevention trial of aspirin among Japanese patients with lacunar infarction for prevention of stroke (332 patients took 300 mg of aspirin per day, and there were 278 controls), aspirin had no effect on prevention of recurrence of stroke.[25] A lack of beneficial effect of aspirin on risk of lacunar infarction is not conclusive because of a wide CI in risk estimates associated with aspirin use. However, the difference in pathogenetic mechanism between this condition and large-artery occlusive infarction may support the lack of effect. Lacunar infarction is caused by occlusion of small penetrating arteries in the internal capsule, corona radiata, basal ganglia, and brain stem. Occlusion of small penetrating arteries can be caused by atherosclerotic plaque of large cerebral arteries at the origin of penetrating arteries[26] or by thrombosis of microaneurysms,[27,28] but it is primarily caused by arteriosclerosis (fibrinoid necrosis) in small penetrating arteries.[27,29] Unlike atherosclerosis, this small-vessel pathology is characterized by the loss of medial smooth muscle cells and degenerative changes of intima with fibrin deposition, macrophage infiltration, and fibroblastic connective tissue replacement by fibrinoid material, which cause occlusion of the vascular lumen.[27,29] Thrombosis involving platelets is not commonly observed in lacunar infarction.[27]

In the present study, we found a 2-fold excess risk of subarachnoid hemorrhage among women who took ≥15 aspirin per week. This excess risk was statistically significant when definite and probable cases were combined but marginally significant when restricted to definite cases. In 1 primary prevention trial with 35 end points, the incidence of hemorrhagic strokes, although not specified as subarachnoid or intraparenchymal hemorrhage, tended to be higher among men taking 325 mg on alternative days compared with the placebo group: RR in the aspirin versus placebo group was 2.14 (95% CI 0.84 to 5.69, $P=0.06$).[3] Our result is consistent with this finding, although we found a significant excess risk only for women taking ≥15 aspirin per week.

An excess risk of subarachnoid hemorrhage with ≥15 aspirin per week is possibly due to the combined inhibitory effects of synthesis of thromboxane A_2 in platelets and prostacyclin in vascular endothelial cells. These combined

TABLE 3. Multivariate Relative Risk (95% CI) of Stroke Subtypes in a Cohort of 79 319 Women From 1980 to 1994, According to Aspirin Use Stratified by Age Group, Hypertensive Status, and Smoking Status

	Aspirin per Week, n				
	0	1–6	7–14	≥15	*P* for Trend
Age 34–54					
Person-years	256 781	247 986	56 033	30 183	
Large-artery occlusive infarction					
Cases	15	8	5	2	
Multivariate RR*	1.0	0.49 (0.20–1.20)	1.25 (0.44–3.51)	...	0.76
Subarachnoid hemorrhage					
Cases	24	25	6	5	
Multivariate RR*	1.0	1.20 (0.67–2.14)	1.12 (0.45–2.77)	1.49 (0.56–3.96)	0.48
Age ≥55					
Person-years	130 357	153 090	46 626	23 121	
Large-artery occlusive infarction					
Cases	26	14	10	2	
Multivariate RR*	1.0	0.50 (0.26–0.98)	0.89 (0.42–1.87)	...	0.34
Subarachnoid hemorrhage					
Cases	13	13	7	7	
Multivariate RR*	1.0	0.81 (0.37–1.76)	1.43 (0.56–3.63)	2.87 (1.12–7.31)	0.008
Nonhypertensives					
Person-years	308 577	312 997	71 629	36 059	
Large-artery occlusive infarction					
Cases	17	11	3	1	
Multivariate RR†	1.0	0.58 (0.27–1.27)	0.59 (0.17–2.05)	...	0.33
Subarachnoid hemorrhage					
Cases	27	23	12	5	
Multivariate RR†	1.0	0.80 (0.45–1.43)	1.83 (0.92–3.66)	1.38 (0.52–3.61)	0.18
Hypertensives					
Person-years	78 561	88 080	31 030	17 245	
Large-artery occlusive infarction					
Cases	24	11	12	3	
Multivariate RR†	1.0	0.42 (0.20–0.87)	1.20 (0.59–2.43)	0.56 (0.17–1.87)	0.85
Subarachnoid hemorrhage					
Cases	10	15	1	7	
Multivariate RR†	1.0	1.61 (0.70–3.68)	...	3.19 (1.19–8.59)	0.06
Nonsmokers					
Person-years	295 953	318 677	80 542	40 898	
Large-artery occlusive infarction					
Cases	20	14	7	1	
Multivariate RR‡	1.0	0.61 (0.30–1.23)	0.86 (0.36–2.08)	...	0.24
Subarachnoid hemorrhage					
Cases	20	20	6	7	
Multivariate RR‡	1.0	0.83 (0.44–1.56)	0.97 (0.38–2.44)	2.10 (0.88–5.05)	0.07
Current smokers					
Person-years	89 977	81 280	21 788	12 275	
Large-artery occlusive infarction					
Cases	21	8	8	3	
Multivariate RR‡	1.0	0.37 (0.16–0.85)	1.14 (0.49–2.61)	0.79 (0.23–2.69)	0.81
Subarachnoid hemorrhage					
Cases	17	18	7	5	
Multivariate RR‡	1.0	1.28 (0.64–2.53)	1.74 (0.71–4.26)	2.03 (0.73–5.61)	0.14

*Adjusted for age (5-year categories); time interval; body mass index (5 categories); alcohol intake (4 categories); menopausal status and postmenopausal hormone use; vigorous exercise (yes vs no); multivitamin use (yes vs no); vitamin E use (yes vs no); histories of hypertension, diabetes, and high cholesterol levels (yes vs no); and intake (quintile) of saturated fat, animal protein, calcium, n-3 polyunsaturated fatty acids, and dietary vitamin C.

†Adjusted for factors cited above except a history of hypertension.

‡Adjusted for factors cited above except smoking status.

effects not only reduce platelet aggregation, thereby leading to an increased bleeding tendency, but also might enhance vasospasm because prostacyclin is a strong vasodilator.[22] An in vitro study using postmortem human arteries[30] demonstrated that prostacyclin reversed contractions of intracranial basilar arteries caused by a vasoconstrictor such as prostaglandin endoperoxide. It is postulated that spasm in basilar arteries may alter hemodynamics in the circle of Willis and increase hemodynamic stress in vulnerable sites for the development and rupture of saccular aneurysms. Unilateral ligation of a carotid artery, which alters hemodynamics in the circle of Willis, is essential to the development of experimental saccular aneurysms,[31] and turbulence of blood flow was demonstrated in vivo in the early stages of aneurysm formation.[32]

Several limitations of this observational study warrant consideration. Women who take 1 to 6 aspirin per week may be at lower risk of cardiovascular disease because of other health habits. In particular, lower prevalence of some of the major cardiovascular risk factors such as diabetes and high cholesterol levels should be taken into account as confounding factors. However, after further adjustment for these cardiovascular risk factors and nutrient intake, the RRs were not appreciably altered. Another possibility is that indications for low-dose aspirin use are themselves associated with reduced risk of stroke. According to supplementary questionnaires mailed to a random sample of 100 participants who reported low-dose aspirin use on the 1980, 1982, or 1984 questionnaire, approximately 80% of them indicated that their reasons for aspirin use were headache and/or musculoskeletal pain, which may not be relevant to reduced stroke risk.[9] Fewer than 10% of the women took aspirin for primary prevention of cardiovascular disease.[9] The absence of a strong relationship between aspirin use and prevalence of cardiovascular risk factors in 1984 also argues against indications for primary prevention in this cohort. Therefore, it is unlikely that indications for low-dose aspirin use are associated with reduced risk of stroke in this cohort. Another limitation is that we had limited number of strokes by stroke subtype in each category of aspirin use (for example, 22 large-artery occlusive infarctions in women who took 1 to 6 aspirin per week), which made it difficult to draw firm conclusions about the stroke subtype analysis. Professional nurses in this cohort tended to have a higher frequency of aspirin use than the general population of US white women aged 45 to 64 years[33]: 40% to 72% in the proportion of ≥1 aspirin per week versus 27% to 35% in the proportion of ≥1 aspirin during the past 2 weeks. According to the nature of the analysis on the relationship between aspirin use and risk of stroke, the results can be generalized despite a difference in the distribution of aspirin use.

It is possible that the underlying indications for aspirin use of ≥15 per week are associated with increased risk of subarachnoid hemorrhage. Some women with unruptured aneurysms in cerebral arteries have chronic headache and may thus be more likely to take aspirin regularly.[23] According to the Oxfordshire Community Stroke Project,[34] 21% of subarachnoid hemorrhage patients had a history of migraine. The prevalence of a history of migraine in this cohort was very low: 0.2% for no aspirin use, 0.2% for 1 to 6 aspirin per week, 0.3% for 7 to 14 aspirin per week, and 0.4% for ≥15 aspirin per week. Among those with a history of migraine, only 1 woman who used no aspirin developed subarachnoid hemorrhage. Thus, it is unlikely that the increased risk of subarachnoid hemorrhage was due to a history of migraines as an indication for aspirin use, although the contribution of indications for other types of headache was uncertain.

Extrapolation of our results from a cohort of women to men requires caution. There is, however, little evidence supporting a sex difference in the pharmacokinetics of aspirin[35] and its effects on synthesis of thromboxane and prostacyclin.[5] Aspirin has been demonstrated to be effective for the secondary prevention of ischemic stroke in both men and women,[36] and in several secondary prevention trials a significant benefit was observed only for men, probably because of a smaller sample size for women.[36–39] Randomized trials are testing the effects of aspirin on primary prevention of stroke,[40] but further observational studies can assess different quantities of aspirin in relation to the risk of stroke.

In conclusion, the present observational study suggests that intake of 1 to 6 aspirin per week is associated with a substantially reduced risk of large-artery occlusive infarction in middle-aged women but intake of ≥15 aspirin per week may increase the risk of subarachnoid hemorrhage. Confirmatory data on the role of aspirin in primary prevention of stroke in women await results of ongoing randomized clinical trials.

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References

1. Anti-Platelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy, I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ*. 1994;308:81–106.
2. Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K, Warlow C, Hafner B, Thompson E, Norton S, Gilliland J, Doll R. Randomized trial of prophylactic daily aspirin in British male doctors. *BMJ*. 1988;296:313–316.
3. The Steering Committee of the Physicians' Health Study Research Group. Final report from the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med*. 1989;321:129–135.
4. Masotti G, Galanti G, Poggesi L, Abbate R, Neri Serneri GG. Differential inhibition of prostacyclin production and platelet aggregation by aspirin. *Lancet*. 1979;2:1213–1217.
5. Patrignani P, Filabozzi P, Patrono C. Selective cumulative inhibition of platelet thromboxane production by low-dose aspirin in healthy subjects. *J Clin Invest*. 1982;69:1366–1372.
6. Patrono C, Ciabattoni G, Patrignani P, Pugliese F, Filabozzi P, Catella F, Davi G, Forni L. Clinical pharmacology of platelet cyclooxygenase inhibition. *Circulation*. 1985;72:1177–1184.
7. Weksler BB, Pett SB, Alonso D, Richter RC, Stelzer P, Subramanian V, Tack-Goldman K, Gray WA Jr. Differential inhibition by aspirin of vascular and platelet prostaglandin synthesis in atherosclerotic patients. *N Engl J Med*. 1983;308:800–805.
8. Paganini-Hill A, Chao A, Ross RK, Henderson BE. Aspirin use and chronic diseases: a cohort study of the elderly. *BMJ*. 1989;299:1247–1250.

9. Manson JE, Stampfer MJ, Colditz GA, Willett WC, Rosner B, Speizer FE, Hennekens CH. A prospective study of aspirin use and primary prevention of cardiovascular disease in women. *JAMA*. 1991;266: 521–527.
10. Stampfer MJ, Willett WC, Colditz GA, Rosner BA, Speizer FE, Hennekcns CH. A prospective study of postmenopausal estrogen therapy and coronary heart disease. *N Engl J Med*. 1985;313:1044–1049.
11. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol*. 1985;122:51–65.
12. Willett WC, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol*. 1986;124:17–27.
13. Stampfer MJ, Willett WC, Speizer FE, Dysert DC, Lipnick R, Rosner B, Hennekens CH. Test of the National Death Index. *Am J Epidemiol*. 1984;119:837–839.
14. Walker AE, Robins M, Weinfeld FD. The National Survey of Stroke: clinical findings. *Stroke*. 1981;119:837–839.
15. Anderson CS, Jamrozik KD, Burvill PW, Chakera TMH, Johnson GA, Stewart-Wynne EG. Determining the incidence of different subtypes of stroke: results from the Perth Community Stroke Study, 1989–1990. *Med J Aust*. 1993;158:85–89.
16. D'Agostino RB, Lee M-L, Belanger AJ, Cupples LA, Anderson K, Kannel WB. Relation of pooled logistic regression to time-dependent Cox regression analysis: the Framingham Heart Study. *Stat in Med*. 1990;9: 1501–1515.
17. Solberg LA, Strong JP. Risk factors and atherosclerosis: a review of autopsy studies. *Arteriosclerosis*. 1983;3:187–198.
18. Reed DM, Resch JA, Hayashi T, MacLean C, Yano K. A prospective study of cerebral artery atherosclerosis. *Stroke*. 1988;19:820–825.
19. Konishi M, Iso H, Komachi Y, Iida M, Shimamoto T, Jacobs DR Jr, Terao A, Baba S, Sankai T, Ito M. Association of serum total cholesterol, different types of stroke, and stenosis distribution of cerebral arteries: the Akita Pathology Study. *Stroke*. 1993;24:954–964.
20. Adams RJ, Carroll RM, Nichols FT, McNair N, Feldman DS, Feldman EB, Thompson WO. Plasma lipoproteins in cortical versus lacunar infarction. *Stroke*. 1989;20:448–452.
21. Giroud M, Boutron MC, Gras P, Gambert P, Lallemant C, Milan C, Essayagh E, Dumas R. Plasma lipoproteins in cortical versus lacunar infarction with or without cardiac arrhythmia, and in transient ischaemic attacks: a case control study. *Neurol Res*. 1992;14:315–320.
22. Heavy DJ, Barrow SE, Hickling NE, Ritter JM. Aspirin causes short-lived inhibition of bradykinin-stimulated prostacyclin production in man. *Nature*. 1985;318:186–188.
23. Miller VT, Rothrock JF, Pearce LA, Feinberg WM, Hart RG, Anderson DC. Ischemic stroke in patients with atrial fibrillation: effect of aspirin according to stroke mechanism. *Neurology*. 1993;43:32–36.
24. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet*. 1993;342:1255–1262.
25. Yamaguchi T. Comprehensive studies of cerebrovascular disorders. In: *Annual Report of the Research on Cardiovascular Diseases, 1992*. Osaska, Japan: National Cardiovascular Center; 1993:50–51, and G18 (English abstract).
26. Fisher CM. Capsular infarcts: the underlying vascular lesions. *Arch Neurol*. 1979;36:65–73.
27. Fisher CM. The arterial lesions underlying lacunes. *Acta Neuropathol (Berl)*. 1969;12:1–15.
28. Benhaiem-Sigaux N, Gherardi R, Salama J, Gray F, Amouroux J, Poirier J. Thrombosis of a saccular microaneurysm causing cerebral (pontine) lacunae. *Acta Neuropathol (Berl)*. 1986;69:332–336.
29. Russell RW. Observations on intracerebral aneurysms. *Brain*. 1963;86: 425–442.
30. Boullin DJ, Buting S, Blaso WP, Hunt TM, Moncada S. Responses of human and baboon arteries to prostaglandin endoperoxides and biologically generated and synthetic prostacyclin: their relevance to cerebral arterial spasm in man. *Br J Clin Pharmacol*. 1979;7:139–147.
31. Handa H, Hashimoto N, Nagata I, Hazama F. Saccular cerebral aneurysms in rats: a newly developed animal model of the disease. *Stroke*. 1983;14:857–866.
32. Nakatani H, Hashimoto N, Kikuchi H, Yamaguchi S, Niimi H. In vivo flow visualization of induced saccular cerebral aneurysms in rats. *Acta Neurochir (Wien)*. 1993;122:244–249.
33. Shahar E, Folsom AR, Romm FJ, Bisgard KM, Metcalf PA, Crum L, McGovern PG, Hutchinson RG, Heis G, for the ARIC Study Investigators. Patterns of aspirin use in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J*. 1996;131:915–922.
34. Henrich JB, Sandercock PAG, Warlow CP, Jones LN. Stroke and migraine in the Oxfordshire Community Stroke Project. *J Neurol*. 1986; 233:257–262.
35. Ho PC, Triggs EJ, Bourne DWA, Heazlewood VJ. The effects of age and sex on the disposition of acetylsalicylic acid and its metabolites. *Br J Clin Pharmacol*. 1985;19:675–684.
36. Bousser MG, Eschwege E, Haguenau M, Lefaucconnier JM, Thibult N, Touboul D, Touboul PJ. "AICLA" controlled trial of aspirin and dipyridamole in the secondary prevention of athero-thrombotic cerebral ischemia. *Stroke*. 1983;14:5–14.
37. The Canadian Cooperative Study Group. A randomized trial of aspirin and sulfinpyrazone in threatened stroke. *N Engl J Med*. 1978;299:53–59.
38. Candelise L, Landi G, Perrone P, Bracchi M, Brambilla G. A randomized trial of aspirin and sulfinpyrazone in patients with TIA. *Stroke*. 1982;13: 175–179.
39. UK-TIA Study Group. The United Kingdom Transient Ischemic Attack (UK-TIA) Aspirin Trial: final results. *J Neurol Neurosurg Psychiatry*. 1991;54:1044–1054.
40. Buring JE, Hennekens CH. The Women's Health Study: summary of the study design. *J Myocardial Ischemia*. 1992;4:27–29.