Alcohol Consumption and Risk of Stroke Among Middle-Aged Men: The JPHC Study Cohort I

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Background and Purpose—The impact of light-to-moderate alcohol consumption on risk of stroke has not been well examined in a single study, although the effect is hypothesized to differ among stroke subtypes from meta-analyses.

Methods—A total of 19,544 men aged 40 to 59 years living in communities were followed-up from 1990 to 1992 to the end of 2001 in the Japan Public Health Center-based Prospective Study on Cancer and Cardiovascular Disease (JPHC Study).

Results—After 214,504 person-years of follow-up, 694 incident strokes were documented, of which 611 were confirmed by imaging studies or autopsy, including 219 intraparenchymal hemorrhages, 73 subarachnoid hemorrhages, and 319 ischemic strokes. Alcohol consumption was positively associated with age-adjusted risk of total stroke with a 68% excess risk among drinkers of ≥450 g ethanol per week compared with occasional drinkers. This excess risk was confined primarily to hemorrhagic stroke, which remained statistically significant even after controlling for hypertension and other cardiovascular risk factors (RR: 2.15; 95% CI: 1.22 to 3.79). There was a lower risk of ischemic stroke, more specifically lacunar infarction, a higher risk of hemorrhagic stroke, and no excess risk of total stroke among drinkers of 1 to 149 g ethanol per week compared with occasional drinkers; the respective multivariate RR (95% CI) was 0.59 (0.37 to 0.93), 0.43 (0.22 to 0.87), 1.73 (0.98 to 3.07), and 0.98 (0.71 to 1.36).

Conclusions—We found differential effects of light-to-moderate alcohol consumption on risks of hemorrhagic and ischemic strokes among middle-aged men. Light-to-moderate alcohol consumption, ie, ≤2 drinks per day, does not raise the risk of total stroke. (Stroke. 2004;35:1124-1129.)

Key Words: alcohol stroke risk factors

Previous review and meta-analysis of case-control and cohort studies1,2 synthesized the hypothesis on the differential effects of alcohol consumption on the risk of hemorrhagic stroke (an adverse effect of moderate-to-heavy drinking3–5) and nonhemorrhagic strokes (a beneficial effect of light-to-moderate drinking4–7).

However, the evidence on these differential effects on risk of stroke subtypes and a net effect on risk of total stroke are still limited, because only 1 study of American female nurses has shown these differential effects in a single cohort.8 Other cohort studies of Americans,9 Japanese Americans,10 Japanese men,11,12 and Chinese men13 showed an adverse effect on risk of hemorrhagic stroke but no effect on risk of ischemic stroke compared with nondrinkers or abstainers.12 Another series of studies of whites14,15 showed reduced risk of ischemic or total strokes among light-to-moderate drinkers but reported no significant effect of moderate-to-heavy drinking on risk of hemorrhagic stroke.

Investigation of middle-aged Japanese men should be of value in identifying the relationship of alcohol consumption with risk of stroke and its subtypes more comprehensively because of their high prevalence of alcohol drinking12,16 and high incidence of stroke.11,12 In addition, that study contributes to formulate public health recommendations about alcohol consumption. We studied this topic using data from a large cohort study.

Materials and Methods

Study Cohort

The Japan Public Health Center (JPHC) Study Cohort I was a population-based sample of 27,063 men and 27,435 women who were born between 1930 and 1949 (age 40 to 59 years) and were

Received August 21, 2003; final revision received January 7, 2004; accepted January 9, 2004.

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Stroke is available at http://www.strokeaha.org DOI: 10.1161/01.STR.0000124459.33597.00

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registered in 14 administrative districts supervised by 4 public health centers (PHC) areas on January 1, 1990.

In the present study, the data for women are not presented because the small number of moderate-to-heavy drinkers in this group. The male population included 6022 from Ninohe City and Karumai Town in the Ninohe PHC area of Iwate Prefecture, 7559 from Yokote City and Omonogawa town in the Yokote PHC area of Akita, 6173 from 8 districts of Minami-Saku County in the Saku PHC area of Nagano, and 7309 men from Gushikawa City and Onna Village in the Ishikawa PHC area of Okinawa. The present study was approved by the Ethical Committee of the National Cancer Center.

Baseline Survey
A self-administered questionnaire was distributed to all registered noninstitutional residents in 1990, asking them to report on their demographic characteristics: height, weight, medical history, smoking and drinking habits, and diet. Of these, 20,665 men (76%) returned their questionnaires between January 1990 and May 1992, primarily between February 1990 and October 1990. Informed consent was obtained from each participant when completing the questionnaire. We excluded men who reported stroke, myocardial infarction, angina pectoris, or cancer at baseline. A total of 19,544 men who reported their alcohol consumption were included in the present analysis.

Alcohol consumption was represented in the questionnaire by the frequency of consumption during the past month and categorized into 6 classes: <1 day/month, 1 to 3 days/month, 1 to 2 days/week, 3 to 4 days/week, 5 to 6 days/week, and every day. Men who reported alcohol consumption at least once per week were asked further details on the usual amount and type of alcohol. Weekly ethanol consumption was calculated by dividing the amount of ethanol per day by the frequency per week. The amount of ethanol was calculated in grams of ethanol as follows: 180 mL sake (rice wine) as 23 g ethanol, 180 mL shochu and awamori (white spirits) as 36 g ethanol, 30 mL whisky or brandy as 10 g ethanol, 60 mL wine as 6 g ethanol, and 633 mL beer as 23 g ethanol. Alcohol consumption was classified into 6 categories: nondrinkers (<1 day/week), occasional drinkers (1 to 3 days/week), weekly alcohol consumption of 1 to 14 g/week, 150 to 299 g/week, 300 to 449 g/week, and ≥450 g/week. Former drinkers were considered nondrinkers in the present study.

The reproducibility of alcohol consumption between 1990 and 1995 was measured by Spearman rank correlation in 94 men (correlation coefficient = 0.69). The validity of alcohol consumption estimation was estimated by Spearman rank correlation, with alcohol consumption based on 4 7-day diet records among 94 men (correlation coefficient = 0.73). Furthermore, mean levels of serum γ-glutamyl transferase in men in the aforementioned 6 alcohol consumption categories were 23, 26, 39, 48, 84, and 90 IU/L, respectively, whereas those of high-density lipoprotein cholesterol were 43, 46, 50, 51, 56, and 58 mg/dL, respectively, after adjustment for age, body mass index, cigarette use, and residential area in our previous study using the same questionnaire in almost the same areas (n = 562).

The frequency of weekly intake of 27 food items was reported under 4 categories: rarely, 1 to 2 days/week, 3 to 4 days/week, and almost every day. The weekly frequency for each food item was calculated according to a score assigned to each frequency category (0, 1.5, 3.5, and 7, respectively). Histories of hypertension and diabetes were ascertained by the question, “Have the following conditions been diagnosed in you by physicians?” with a list of hypertension, diabetes, and other chronic diseases.

Confirmation of Stroke and Classification of Stroke Subtypes
We registered a total of 25 hospitals facilitated by computer tomographic scan and/or magnetic resonance images in the 4 PHC areas (n of hospitals = 8 for the Ninohe PHC area, 3 for the Saku PHC area, and 11 for the Ishikawa PHC area). They were all major hospitals where acute stroke cases would be admitted. Medical records were reviewed by registered hospital workers or PHC physicians, blinded to the lifestyle data. Stroke events were registered if they occurred after the date of return of the baseline questionnaire and before January 1, 2002.

To complete surveillance for fatal stroke, we also conducted systematic search for death certificates. For all fatal strokes (International Classification of Diseases, 9th Revision [ICD-9] 430 to 438) listed on the death certificate but that had not been registered, medical records in registered hospitals were reviewed by hospital workers, PHC physicians, or research physician–epidemiologists. When no medical records were available (death certificate information only), we regarded these fatal strokes as probable strokes (24% of fatal strokes).

For nonfatal strokes, we asked by letter or telephone about the onset of stroke and for permission to review the medical records for 274 persons who reported history of nonfatal stroke on the 10-year follow-up questionnaire (88% followed-up) and had not been registered as stroke cases. Of these 274, 233 (85%) persons were reached, and 169 of them reported confirmatory information of stroke. Of these 169, 151 (99%) persons provided permission to review their medical records. All of these medical records were reviewed by hospital workers, PHC physicians, or research physicians; 104 cases were found to be defined as stroke based on imaging studies. Nonfatal strokes for which confirmatory information was obtained by letter or telephone, but for which no medical records were available, were regarded as probable (2% of nonfatal strokes). Subjects who reported history of nonfatal stroke on the 10-year follow-up questionnaire, but had not been confirmed as stroke, were regarded as nonstroke. For the analyses of total stroke, both confirmed and probable strokes were used.

Strokes were confirmed according to the criteria of the National Survey of Stroke, which requires a constellation of neurological deficits of sudden or rapid onset lasting at least 24 hours or until death. For each subtype of stroke, ie, subarachnoid hemorrhage, intraparenchymal hemorrhage, ischemic stroke (thrombotic or embolic stroke), a definite diagnosis was established based on examination of computer tomographic scan, magnetic resonance images, or autopsy. All definite thrombotic strokes were further classified as large-artery occlusive infarction, lacunar infarction, or unclassified thrombotic infarction according to the criteria applied to the Nurses’ Health Study. Changes in residence status were identified through the residential registry in each area. Subjects who moved from their original residential areas (2% of the total participants) were treated as censored at that time.

Statistical Analysis
Statistical analyses were based on incidence rates of stroke during the 11.0 years of follow-up from 1990 to the end of 2001. For each man, person-months of follow-up were calculated from January 1, 1990 to the first endpoint, death, emigration, or January 1, 2002, whichever was first. The relative risk of stroke was defined as the incidence of stroke among men in 5 categories of alcohol consumption (nondrinkers, current drinkers of 1 to 149, 150 to 299, 300 to 449, and ≥450 g/d) divided by the corresponding rate among occasional drinkers. We did not choose nondrinkers as the reference, because using our questionnaire we could not discriminate never-drinkers from past drinkers who were likely to have ill health. Instead, we chose occasional drinkers as the reference, because men in this category may be less likely to have had alcohol-related health conditions or preclinical disorders that increase the incidence of stroke. Differences in age-adjusted mean values or prevalence of risk characteristics at baseline according to alcohol consumption were tested using the analysis of covariance.

To examine a shorter-term effect (5 years) of alcohol consumption on the risk of stroke for the secondary analysis, we updated the data of alcohol consumption estimated in the 5-year follow-up questionnaire survey, to which 90% of the baseline participants responded. The relative risk with 95% confidence intervals was calculated after adjusting for age and other potential confounding factors using the conventional and time-dependent Cox proportional hazards models.
A test for linear trend across the alcohol categories was conducted by assigning median values for each category testing the significance of this variable.

Potential confounding factors for the adjustment were baseline values of age, smoking status, body mass index, history of diabetes, education level, sports at leisure time, and dietary intake categories of fruits, total vegetables, and fish. History of hypertension was regarded as a mediator in the causal pathway between alcohol consumption and stroke. Then, we constructed the model with further adjustment for history of hypertension as well as the confounding variables to examine the residual or independent effect of alcohol consumption on risk of stroke. All statistical analyses were conducted using SAS (version 8.02).

**Results**

During an average follow-up period of 11.0 years, 694 total strokes were documented, of which 611 were confirmed by imaging studies or autopsy. They comprised 219 intraparenchymal hemorrhages, 73 subarachnoid hemorrhages, and 319 ischemic strokes (141 lacunar infarctions, 54 large-artery occlusive infarctions, 85 embolic infarctions, and 39 unclassified ischemic strokes).

Occasional drinkers were 0.2 to 0.6 years younger on average than current drinkers and 1.1 years younger than nondrinkers (Table 1). Mean body mass index was higher among occasional drinkers and drinkers of 1 to 149 g ethanol per week than among those in other alcohol categories. The proportions of nonsmokers, those with high education, sport at leisure time of ≥1 day per week, and the frequency of fruit intake were highest among drinkers of 1 to 149 g ethanol per week and occasional drinkers, and lowest among drinkers of ≥450 g ethanol per week. The prevalence of hypertension and the frequency of fish intake were highest among drinkers of ≥450 g ethanol per week, and progressively lower with the lower alcohol consumption.

Alcohol consumption was positively associated with age-adjusted risk of total stroke (Table 2). This association did not change materially after adjustment for smoking status, body mass index, diabetes, education level, sport activity, intakes of selected foods, and public health center areas. There was a significant excess risk of total stroke among drinkers of ≥450 g ethanol per week. After further adjustment for hypertension, the excess risk was reduced but remained statistically significant. The excess risk among heavy drinkers was confined primarily to hemorrhagic stroke, particularly intraparenchymal hemorrhage, and was not abolished by further adjustment for hypertension.

There was a lower risk of ischemic stroke among drinkers of 1 to 149 g ethanol per week than occasional drinkers; the multivariate relative risk after further adjustment for hypertension and other cardiovascular risk factors was 0.59 (95% CI: 0.37 to 0.93). This risk reduction was found for each subtype of ischemic stroke, particularly evident for lacunar infarction.

Figure 1 illustrates the differential effects of alcohol consumption on risks of hemorrhagic and ischemic strokes after adjustment for cardiovascular risk factors other than hypertension. Regardless of the update for alcohol consumption, there was a positive association between alcohol consumption and risk of hemorrhagic stroke and a reduced risk of ischemic stroke among light-to-moderate drinkers.

**Discussion**

We showed in a large prospective study of middle-aged Japanese men the presence of a positive linear relationship...
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<th>N of Cases</th>
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<td>N of cases</td>
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<td>0.80 (0.36-2.18)</td>
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Multivariate RR adjusted for age (5-year categories), cigarette smoking (never, former, and current 1–19 and ≥20 cigarettes per day), body mass index (quintiles), history of diabetes (yes), education level (junior high school, high school, and college or more), sports at leisure time (< 1 d/wk, 1–3 d/wk, and ≥1 d/wk), frequency (1 d/wk, 1–2 d/wk, 3–4 d/wk, and ≥5 d/wk) of fruit, vegetable, and fish servings, and public health centers.
between alcohol consumption and the risk of total stroke. Approximately 60% excess risk of total stroke was observed among heavy drinkers of \( \geq 450 \) g ethanol per week compared with occasional drinkers after adjustment for known cardiovascular risk factors and selected lifestyle variables. However, the further adjustment for hypertension attenuated the relation, which suggested hypertension as a primary mediator for the stroke risk.

For hemorrhagic stroke, the excess risk associated with heavy drinking of \( \geq 450 \) g and drinking of 150 to 449 g ethanol per week remained apparent even after controlling for hypertension. The sustained excess risk of hemorrhagic stroke associated with heavy drinking strongly suggests that the excess risk may be mediated not only by high blood pressure but also by other mechanisms. They included reduced platelet aggregation and enhanced fibrinolysis via increased secretion of plasminogen activator from endothelial cells. The excess risk with moderate drinking may be in part caused by the underreporting of alcohol consumption among heavy drinkers.

To our knowledge, this study is the first to show a reduced risk of ischemic stroke with light-to-moderate alcohol consumption and an increased risk of hemorrhagic stroke with moderate-to-heavy drinking in the same cohort of men. The number of ischemic strokes was large and the association did not change materially after adjustment for known cardiovascular risk factors and selected lifestyles. The reduced risk of ischemic stroke even after adjustment for hypertension suggests that this relation was unlikely mediated by hypertension. The potential mechanisms for this risk reduction included increased serum high-density lipoprotein cholesterol concentration, reduced platelet aggregation, enhanced fibrinolysis, and reduced plasma fibrinogen levels. Potential effects of reduced oxidation of low-density lipoprotein by polyphenolic components of red grape wine are minimal, because in the present study <0.1% of the participants reported drinking grape wine whereas 42% reported drinking sake, 26% drinking beer, 24% drinking a Japanese hard liquor, and 10% drinking whisky. Our findings could be applicable to middle-aged men of other ethnicity because they were consistent with a priori hypothesis based on sound mechanisms.

A potential limitation of our study is the residual uncontrolled confounding of the association between alcohol consumption and risk of stroke. For example, light-to-moderate drinking may be a marker of a healthy lifestyle. Drinkers of 1 to 149 g ethanol per week smoked less, exercised more, and ate more fruits than men of other alcohol categories. Although we controlled for these lifestyle variables in our multivariate model, we cannot exclude the possibility that some residual confounding by other lifestyles and risk factors remains. Also, the data on hypertension and diabetes were self-reported, although the prevalence of undetected hypertension and diabetes may be small because of nationwide health screenings in Japan. Lastly, the generalizability of our findings to women and older men is uncertain.

In conclusion, the present study provided epidemiological evidence on the differential effects of alcohol consumption on risk of hemorrhagic and ischemic strokes. Compared with occasional drinkers, heavy drinkers of \( \geq 450 \) g ethanol per week (\( \geq 6 \) drinks per day) had a 1.5- to 2-fold excess risk of total and hemorrhagic strokes. Drinkers of 1 to 149 g ethanol per week (\( \leq 2 \) drinks) were at a 40% reduced risk of ischemic stroke. Thus, for the prevention of stroke, it would be a practical approach to advise the reduction of alcohol consumption among heavy drinkers and to permit the maintenance of alcohol consumption among light-to-moderate drinkers, unless clinical or social problems outweigh potential benefits.

**Acknowledgments**

This study was supported by grants-in-aid for Cancer Research and for the Second Term Comprehensive Ten-Year Strategy for Cancer Control from the Ministry of Health, Labor, and Welfare of Japan. The authors thank all staff members in each study area and in the central office for their painstaking efforts to conduct the baseline survey and follow-up, and Dr Aaron R. Folsom, University of Minnesota, for his valuable comments on the manuscript.

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Stroke. 2004;35:1124-1129; originally published online March 11, 2004;
doi: 10.1161/01.STR.0000124459.33597.00

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