Milk and Dairy Consumption and Risk of Dementia in an Elderly Japanese Population: The Hisayama Study

Mio Ozawa, PhD, Tomoyuki Ohara, MD, PhD,*† Toshiharu Ninomiya, MD, PhD,‡ Jun Hata, MD, PhD,*‡ Daigo Yoshida, PhD,* Naoko Mukai, MD, PhD,*‡ Masaharu Nagata, MD, PhD,*‡ Kazuhiro Uchida, PhD,§ Tomoko Shirota, PhD,§ Takanari Kitazono, MD, PhD,‡ and Yutaka Kiyohara, MD, PhD**

OBJECTIVES: To determine the effect of milk and dairy intake on the development of all-cause dementia and its subtypes in an elderly Japanese population.

DESIGN: Prospective cohort study.

SETTING: The Hisayama Study, Japan.

PARTICIPANTS: Individuals aged 60 and older without dementia (N = 1,081).

MEASUREMENTS: Milk and dairy intake was estimated using a 70-item semiquantitative food frequency questionnaire grouped into quartiles. The risk estimates of milk and dairy intake on the development of all-cause dementia, Alzheimer's disease (AD), and vascular dementia (VaD) were computed using a Cox proportional hazards model.

RESULTS: Over 17 years of follow-up, 303 subjects developed all-cause dementia; 166 had AD, and 98 had VaD. The age- and sex-adjusted incidence of all-cause dementia, AD, and VaD significantly decreased as milk and dairy intake level increased (P for trend = .03 for all-cause dementia, .04 for AD, .01 for VaD). After adjusting for potential confounders, the linear relationship between milk and dairy intake and development of AD remained significant (P for trend = .03), whereas the relationships with all-cause dementia and VaD were not significant. The risk of AD was significantly lower in the second, third, and fourth quartiles of milk and dairy intake than in the first quartile.

CONCLUSION: Greater milk and dairy intake reduced the risk of dementia, especially AD, in the general Japanese population. **J Am Geriatr Soc 2014.**

From the *Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, †Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, ‡Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, and §Department of Health Promotion, School of Health and Nutrition Sciences, Nakamura-Gakuen University, Fukuoka, Japan.

Address correspondence to Tomoyuki Ohara, Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, 3–1-1 Maidashi, Higashi-ku, Fukuoka 812–8582, Japan. E-mail: ohara77@envmed.med.kyushu-u.ac.jp

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The increasing prevalence of dementia worldwide is a major public health concern. According to the World Health Organization and Alzheimer's Disease International, the number of people living with dementia will double by 2030 and more than triple by 2050,[1] but the causes of dementia, especially Alzheimer's disease (AD), remain unclear, and there are no disease-modifying therapies. Thus, there is an urgent need to identify factors that can prevent development of dementia to decrease the burden of this disease. Diet is one of the factors that can be modified, and it may have a protective influence against dementia. Milk and dairy intake has been reported to decrease cerebrovascular risk factors, such as hypertension,[2] diabetes mellitus,[3] and obesity,[4] which are associated with the development of dementia,[5] but a limited number of epidemiological studies have assessed the relationship between milk and dairy intake and cognitive impairment or dementia.[6–12] To this end, a community-based prospective cohort study was established to evaluate risk factors for or protective factors against dementia in the Japanese population. A feature of this study is that the subtypes of dementia have been verified using detailed neurological and morphological examination, including neuroimaging and autopsy. The purpose of this study was to elucidate the relationship between milk and dairy intake and the development of dementia and its subtypes in an elderly Japanese population.

METHODS

Study Populations

The Hisayama Study is an ongoing population-based prospective cohort study in the town of Hisayama, a suburb

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of the Fukuoka metropolitan area in the southern part of Japan.[13] This study was begun in 1961 to determine the prevalence and incidence of cerebro- and cardiovascular diseases and their risk factors in Japanese. Data from the national census and nutrition survey indicate that the age and occupational distributions and nutrient intake of the population of Hisayama are similar to those of Japan as a whole for each year from 1961 to the present.[14] Full community surveys of the health status and neurological condition of residents aged 40 and older have been repeated every 1 to 2 years since 1961. Comprehensive surveys of cognitive impairment have also been performed every 6 or 7 years in the elderly adults of the town since 1985.[15,16] In 1988, 1,228 residents aged 60 and older (participation rate 91.1%) underwent a screening examination for the present study. After excluding 35 subjects who already had dementia at baseline, 111 subjects whose dietary questionnaires were not available, and one subject with no blood sample, 1,081 subjects (457 men, 624 women) were enrolled in this study.

Follow-Up Survey

The subjects were followed prospectively for 17 years, from December 1988 to November 2005, during which time health examinations were repeated every 1 to 2 years.[13] Letters or telephone calls were used to collect the health information of subjects who did not have examinations or who had moved out of town. A daily monitoring system was also established with the study team and local physicians or members of the town's Health and Welfare Office to collect information about new events, including stroke, cognitive impairment, and dementia. Follow-up screening surveys of cognitive function, including neuropsychological tests (the Hasegawa Dementia Scale,[17] the Hasegawa Dementia Scale—Revised,[18] or the Mini-Mental State Examination[19]), were conducted in 1992, 1998, and 2005. The study physician and psychiatrist carefully evaluated any subject suspected of having new neurological symptoms, including cognitive impairment, by conducting a comprehensive investigation including interviews of the family or attending physician, physical and neurological examinations, and a review of the clinical records. Furthermore, when a subject died, all the available clinical information was reviewed, the attending physician and family of the deceased were interviewed, and an attempt was made to obtain permission for an autopsy from the family. During follow-up, 518 subjects died, 387 (74.7%) of whom underwent brain examination at autopsy. No subjects were lost to follow-up.

Diagnosis of Dementia

The guidelines of the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*, were used to define the diagnosis of dementia,[20] the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association were used to define subjects with AD,[21] and the criteria of the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences were used to determine the diagnoses of vascular dementia (VaD).[22] Clinical information, including neuroimaging, was used to diagnose possible and probable dementia subtypes. Definite dementia subtypes were also determined on the basis of clinical and neuropathological information in subjects with dementia who underwent autopsy. The diagnostic procedure for autopsy cases has been previously reported.[23] A neuropathological diagnosis of AD was made following the National Institute on Aging—Reagan Institute criteria;[24] the frequency of neuritic plaques and neurofibrillary tangles was evaluated using the Consortium to Establish a Registry for Alzheimer's Disease criteria[25] and Braak stage.[26] Definite VaD cases were confirmed with causative stroke or cerebrovascular change and no neuropathological evidence of other forms of dementia. Expert stroke physicians and psychiatrists adjudicated each case of dementia.

During the 17 years of follow-up, 303 subjects (103 men, 200 women) developed dementia; 261 (86.1%) were evaluated using brain imaging, 155 (51.2%) underwent autopsy, and both were performed in 143. Thus, 273 subjects (90.0%) had some kind of morphological examination. Of subjects with dementia cases, 25 with AD and 18 with VaD had other, coexisting subtypes of dementia, 14 of which were a mixed type of AD and VaD. These cases were counted as events in the analyses for each subtype. Finally, 166 subjects had AD (77 definite AD, 68 probable AD, 21 possible AD), and 98 had VaD (63 definite VaD, 35 probable VaD).

Nutritional Survey

The dietary survey was conducted using a 70-item semiquantitative food frequency questionnaire (SFFQ) concerning food intake.[27] Average food intake per day was calculated from the weekly frequency of various foods and the amount (quantity) of each food portion. The validity of this questionnaire has been reported previously.[28] Briefly, 65 subjects were randomly selected from 981 individuals aged 40 and older who underwent a health examination in 1987. Information regarding food intake was collected for 7 successive days using a weighted food record. Similarly, information regarding food intake was collected from the same subjects using the SFFQ. As a result, the 1-day average intake of milk and dairy products based on SFFQ was 84.6 g, and that based on the weighted food record was 103.9 g. The correlation coefficient in the amount of milk and dairy intake between the SFFQ and weighted food record was 0.53 ($P < .001$); this correlation was considered moderate.

The questionnaire was administered before initiation of this study; a trained dietician or nutritionist questioned each participant in the screening examination. Nutritional intake was calculated using the *Standard Tables of Food Composition in Japan, Fourth Revision*.[29] Each food group was adjusted for energy intake using the residual method.[30]

Risk Factor Measurements

At the baseline survey, each subject was asked to complete a self-administered questionnaire covering medical history, antidiabetes and antihypertensive treatments, educational status, smoking habits, alcohol consumption, and physical

activity. History of stroke was defined as a preexisting sudden onset of nonconvulsive and focal neurological deficit persisting for longer than 24 hours on the basis of all available clinical data. Low educational level was defined as less than 7 years of formal education. Smoking habits and alcohol consumption were categorized as current use or no current use. Regular exercise was defined as engaging in sports more than three times a week during leisure time. Blood pressure was measured three times using a standard mercury sphygmomanometer in the sitting position after at least 5 minutes rest. The mean of three measurements was used for the analysis. Hypertension was defined as blood pressure of 140/90 mmHg or greater or current use of antihypertensive drugs. Body height and weight were measured in light clothing without shoes, and body mass index (kg/m^2) was calculated. Diabetes mellitus was defined as fasting plasma glucose of 7.0 mmol/L or more, 2-hour postload glucose concentrations or postprandial glucose concentrations of 11.1 mmol/L or more, or current use of insulin or oral medication for diabetes mellitus. Serum total cholesterol levels were measured enzymatically.

Statistical Analysis

Subjects were grouped into quartiles based on amount of milk and dairy intake per day, according to sex. The quartiles for milk and dairy intake were less than 45, 45 to 96, 97 to 197, and 198 g/d or more for women and less than 20, 20 to 75, 76 to 173, and 174 g/d or more for men. The trends in the mean values of risk factors for the milk and dairy intake levels were tested using linear regression and the frequencies using logistic regression analysis. Participants were censored at date of death or end of follow-up for survival analyses. The incidence of dementia was calculated using a person-year method and adjusted for age and sex using the direct method using 10-year age groups of the overall study population. The age- and sex-adjusted or multivariable-adjusted hazard ratios (HRs) with their 95% confidence intervals (CIs) were estimated using the Cox proportional hazards model. The assumption of proportional hazards was checked graphically using log cumulative hazard plots for outcomes according to milk and dairy intake levels. In the multivariable-adjusted model, 15 covariates known to be potential risk or protective factors for dementia were selected: age; sex; low education; history of stroke; hypertension; diabetes mellitus; total cholesterol; body mass index; smoking habits; regular exercise; and energy, vegetable, fruit, fish, and meat intake.[31] Heterogeneity in the relationship between subgroups was tested by adding multiplicative interaction terms to the relevant Cox model. Two-sided $P < .05$ was considered statistically significant in all analyses. SAS version 9.3 (SAS Institute, Inc., Cary, NC) was used to perform all statistical analyses.

Ethical Considerations

This study was conducted with the approval of the Kyushu University institutional review board for clinical research. Written informed consent was obtained from participants.

RESULTS

The baseline characteristics of subjects according to milk and dairy intake levels are summarized in Table 1. Mean age and total cholesterol levels and frequencies of diabetes mellitus and regular exercise were higher with higher milk and dairy intake levels, whereas mean systolic blood pressure and frequencies of hypertension, smoking habits, and alcohol consumption were lower with higher milk and dairy intake levels. In relation to dietary factors, subjects in the fourth quartile of milk and dairy intake ate more fruit and had lower intake of fish and meat than those in the first quartile.

Figure 1 shows the age- and sex-adjusted incidence of all-cause dementia, AD, and VaD according to quartiles of milk and dairy intake levels. The age- and sex-adjusted incidence of all-cause dementia, AD, and VaD was significantly lower with higher milk and dairy intake levels (P for trend = .03 for all-cause dementia, = .04 for AD, and = .01 for VaD).

Table 2 shows the estimated HRs and 95% CIs for the development of dementia and its subtypes according to milk and dairy intake level. There was a significant inverse relationship between milk and dairy intake level and age- and sex-adjusted HR of all-cause dementia (P for trend = .03). This linear relationship did not remain significant after adjustment for age; sex; low education; diabetes mellitus; hypertension; total cholesterol; history of stroke; body mass index; smoking habits; regular exercise; and total energy, vegetable, fruit, fish, and meat intake (P for trend = .09), but the risk of all-cause dementia remained significantly lower in the third quartile than in the first quartile (adjusted HR = 0.69, 95% CI = 0.50–0.96).

With regard to dementia subtypes, multivariable-adjusted HRs of AD were significantly lower with higher milk and dairy intake, but no such relationship was observed for VaD (P for trend = .03 for AD; P for trend = .14 for VaD). The multivariable-adjusted HR of AD was significantly lower in subjects in the second, third, and fourth quartile of milk and dairy intake than in those in the first quartile (adjusted HR = 0.64, 95% CI = 0.41–0.99 for the second quartile; adjusted HR = 0.57, 95% CI = 0.37–0.87 for the third quartile; adjusted HR = 0.63, 95% CI = 0.41–0.98 for the fourth quartile). Although the age- and sex-adjusted HR of VaD was significantly lower in subjects in the fourth quartile of milk and dairy intake than in those in the first quartile, this relationship was not significant after multivariable adjustment (adjusted HR = 0.69, 95% CI = 0.37–1.29 for the fourth quartile). There was no evidence of heterogeneity between men and women in the risk of dementia and its subtypes.

DISCUSSION

This long-term prospective study of an elderly Japanese population demonstrated a significant inverse relationship between milk and dairy intake and risk of development of all-cause dementia, AD, and probably VaD. This is, to the best of the authors' knowledge, the first prospective cohort study to investigate the protective relationship between milk and dairy intake and risk of dementia and its subtypes.

Table 1. Baseline Characteristics of Subjects According to Quartile of Milk and Dairy Consumption: The Hisayama Study, 1988

Characteristic	Q1 (Low), n = 270	Q2, n = 270	Q3, n = 271	Q4 (High), n = 270	*P* for Trend
Female, %	57.8	57.8	57.6	57.8	.99
Age, mean ± SD	68.6 ± 6.4	69.8 ± 6.4	68.9 ± 6.1	70.4 ± 6.8	.008
Education ≤6 years, %	12.0	16.8	11.2	12.0	.56
History of stroke, %	4.1	4.4	4.4	4.4	.84
Systolic blood pressure, mmHg, mean ± SD	142 ± 24	138 ± 23	139 ± 21	137 ± 21	.02
Diastolic blood pressure, mmHg, mean ± SD	77 ± 11	76 ± 11	77 ± 10	75 ± 10	.10
Hypertension, %	57.8	53.7	53.5	48.5	.04
Diabetes mellitus, %	11.5	13.7	14.4	20.0	.007
Total cholesterol, mg/dL, mean ± SD	200 ± 42	204 ± 45	213 ± 43	220 ± 43	<.001
Body mass index, kg/m^2, mean ± SD	22.3 ± 3.1	22.1 ± 3.2	22.5 ± 3.2	22.4 ± 2.7	.40
Smoking habits, %	27.4	23.7	22.9	19.3	.03
Alcohol consumption, %	30.0	26.7	27.7	20.4	.02
Regular exercise, %	13.7	10.0	13.7	21.5	.005
Dietary intake, mean ± SD					
Energy, kcal/d[a]	1,703 ± 402	1,509 ± 395	1,721 ± 400	1,605 ± 372	.44
Vegetable, g/d[a]	251 ± 118	242 ± 102	257 ± 124	256 ± 128	.30
Fruit, g/d[a]	69 ± 69	74 ± 69	91 ± 93	84 ± 64	.002
Fish, g/d[a]	43 ± 43	41 ± 28	36 ± 28	37 ± 22	.006
Meat, g/d[a]	22 ± 24	20 ± 14	19 ± 15	19 ± 15	.03

Quartiles for milk and dairy intake were <45, 45–96, 97–197, ≥198 g/d for women and <20, 20–75, 76–173, ≥174 g/d for men.
SD = standard deviation.
[a]All food groups were adjusted for energy intake using the residual method.

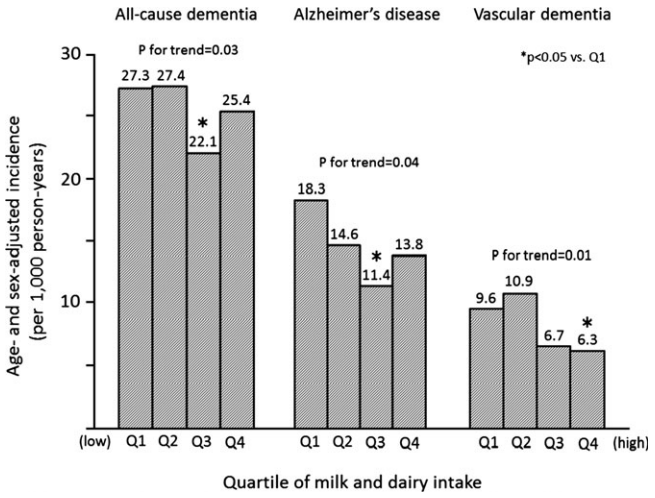

Figure 1. Age- and sex-adjusted incidence of all-cause dementia, Alzheimer's disease, and vascular dementia according to quartile of milk and dairy intake at baseline, 1988–2005.

Several epidemiological studies have investigated the relationship between milk and dairy intake and cognitive impairment or dementia.[6–12] Some cross-sectional studies have evaluated this relationship and found that higher milk and dairy intake is likely to have a protective effect against cognitive impairment.[6–8] A study in Australia demonstrated that low-fat milk and dairy consumption was associated with significantly lower likelihood of poor cognitive function but found the opposite to be true for whole-fat cream and ice cream rich in fat.[9] Similarly, a few prospective studies conducted in Western countries have reported that higher consumption of full-cream milk, milk and dairy desserts, and ice cream increased the risk of cognitive decline.[10,11] These results suggest that low-fat milk and dairy intake might have a more-favorable influence on cognitive function, especially in Western populations, although only one study has evaluated the relationship between milk intake and the risk of dementia longitudinally; the Adult Health Study with atomic bomb survivors in Japan retrospectively evaluated the relationship between milk intake, assessed 25 to 30 years earlier, and the prevalence of AD and VaD. The study concluded that subjects who consumed milk every day had significantly lower prevalence of VaD, but not of AD, than those who consumed milk twice a week or less.[12] This finding is inconsistent with that of the current study, but because the current study and the Adult Health Study had different designs (prospective vs retrospective), the heterogeneity of the methods may explain the discrepancy.

A few cohort studies in Western countries have found that it is possible that the Mediterranean dietary pattern provides protection against dementia, especially AD.[32,33] This diet recommends low to moderate consumption of milk and dairy products. Again, this is a finding that is inconsistent with that of the present study, although in a previous study of the present cohort, the greater adherence to the dietary pattern derived using a reduced rank regression analysis, which was characterized by high intake of milk and dairy products, was associated with a lower risk of dementia.[34] According to data from the Food and Agriculture Organization of the United Nations, there has consistently been a clear difference in the amount of milk and

Table 2. Likelihood of Development of All-Cause Dementia, Alzheimer's Disease, and Vascular Dementia According to Quartile of Milk and Dairy Consumption, 1988–2005

Outcome	Q1 (Low), n = 270	Q2, n = 270	Q3, n = 271	Q4 (High), n = 270	*P* for Trend
All-cause dementia					
Events, n	82	77	67	77	
HR (95% CI)[a]	1.0	0.90 (0.66–1.22)	0.66 (0.48–0.91)	0.76 (0.56–1.04)	.03
HR (95% CI)[b]	1.0	0.85 (0.62–1.18)	0.69 (0.50–0.96)	0.80 (0.57–1.11)	.09
Alzheimer's disease					
Events, n	49	38	37	42	
HR (95% CI)[a]	1.0	0.72 (0.47–1.10)	0.58 (0.38–0.89)	0.68 (0.45–1.03)	.04
HR (95% CI)[b]	1.0	0.64 (0.41–0.99)	0.57 (0.37–0.87)	0.63 (0.41–0.98)	.03
Vascular dementia					
Events, n	28	30	21	19	
HR (95% CI)[a]	1.0	1.04 (0.62–1.74)	0.65 (0.37–1.15)	0.54 (0.30–0.98)	.01
HR (95% CI)[b]	1.0	1.02 (0.59–1.77)	0.74 (0.42–1.33)	0.69 (0.37–1.29)	.14

HR = hazard ratio; CI = confidence interval.

[a]Adjusted for age and sex.

[b]Adjusted for age; sex; low education; history of stroke; hypertension; diabetes mellitus; total cholesterol; body mass index; smoking habits; regular exercise; and energy, vegetable, fruit, fish, and meat intake.

dairy consumption in Japan and Western countries; consumption in the Japanese population is historically approximately half that of Western populations.[35] This evidence, together with the findings of the present study, suggest that the difference in the amount of milk and dairy consumed in Japan and in Western countries could be the reason for the discrepancy in the influence of these foods on the risk of dementia between the populations. In populations with low intake of milk and dairy, such as the Japanese, a "high" intake of these foods is considered to reduce the risk of dementia. Further investigation is needed to clarify this in other ethnic populations.

In the present study, the age- and sex-adjusted HR of VaD was significantly lower in subjects in the fourth quartile of milk and dairy intake than in the first quartile, but this relationship was attenuated after adjustment for other covariates. This finding may have been due to the small number of VaD cases. In addition, because the frequencies of other known cerebrovascular risk factors, such as hypertension and smoking habits, were low in the fourth quartile of milk and dairy intake (Table 1), the risk of VaD may have appeared to decrease in this quartile through mediation of these risk factors.

There are presumably mechanisms for the protective influence of dairy intake against the risk of dementia. In several prospective studies, higher intake of milk and dairy was associated with lower risk of developing stroke and its risk factors, such as hypertension,[2] diabetes mellitus,[3] and obesity,[4] and these same factors were also recognized as risk factors for dementia.[5] Therefore, it is possible that milk and dairy intake decreases the risk of dementia, especially VaD, through mediating these risk factors. Another possible mechanism could be the benefits from some of the nutritional components of milk and dairy. It was previously reported that calcium and magnesium, which are components of milk and dairy, reduced the risk of development of dementia.[36] Milk and dairy consumption is also an important source of vitamin B_{12}, which is known to reduce plasma homocysteine levels. Because low serum vitamin B_{12} levels and high plasma homocysteine levels are reported risk factors for the development of dementia, especially AD,[37,38] milk and dairy consumption could decrease risk because of the influence of these nutrients.[39] Whey protein, another component of milk and dairy products, may also have favorable influence against dementia by reducing fat and improving insulin resistance.[40,41]

The strengths of the current study include its longitudinal, population-based, prospective design; the long follow-up period; perfect follow-up of subjects; and the ability to perform a morphological examination of the brains of most dementia cases using autopsy and neuroimaging, although some potential limitations should be noted. Information regarding the intake of dietary nutrients derived from a semiquantitative food frequency questionnaire may not be fully valid. In addition, the dietary assessment was performed only once, at baseline. These limitations are likely to have introduced some misclassification of food intake, and such misclassifications would weaken the relationship found in the study, biasing the results toward the null hypothesis. Finally, because dairy products are not part of traditional Japanese diets and represent a degree of westernization of lifestyle, the possibility of bias introduced by unmeasurable confounding factors cannot be eliminated.

In conclusion, these findings emphasize the need to consider higher intake of milk and dairy as a potentially protective factor against all-cause dementia, AD, and probably VaD in an elderly Japanese population. Further research will be necessary to clarify the relationship between milk and dairy intake and the risk of developing all-cause dementia and its subtypes in other prospective cohort studies and intervention trials.

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