Cigarette smoking and risk of disabling dementia in a Japanese rural community:

a nested case-control study

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ABSTRACT

Background: Previous prospective cohort studies have examined the association between smoking and the risk of dementia, but the results were inconsistent. *Methods*: A prospective, nested, case-control study was conducted to examine the association between cigarette smoking and risk of disabling dementia within the cohort of 6,343 men and women aged 35–85 years. Incident dementia was documented in 208 men and women (95 cases with and 113 cases without history of stroke). Two control subjects per case were selected by matching for sex, age and year of examination. *Results*: The multivariable odds ratios (95% CI) for current versus never-smokers were 2.3 (1.1-4.7) for total dementia, 2.6 (0.8-8.2) for dementia with history of stroke and 2.2 (0.8-5.7) for dementia without it, yielding no effect of stroke history on the smoking-dementia association. A dose-response relationship was noted between the years of cigarettes smoking and the risk of total dementia and a significant excess risk was found for smokers of ≥ 45 years in duration. *Conclusions*: The present prospective study suggests that a long-term cigarettes smoking may raise the risk of disabling dementia.

Background

Dementia has become a major health problem in Japan, as well as in Western countries, because of the sharp increase in the number of elderly individuals.[1] Stroke produces decline in cognitive functions and dementia [2], and the traditional risk factors for cardiovascular disease, such as hypertension [2-5], high cholesterol [3,5], and diabetes [2,5] are associated with increased risks for both Alzheimer's disease and vascular dementia. By contrast, the contribution of smoking, major risk factor for cardiovascular disease, to dementia is less clear. Several previous case–control studies have indicated that smoking is associated with a reduced risk of dementia.[6] However, this inverse association between smoking and dementia might have been caused by the introduction of differential survival biases.[6,7] Smokers are likely to have been under-represented in these studies because of their increased risk of early death from cardiovascular disease and cancer.[8] In addition, individuals with dementia might have tended to under-report their smoking habits.[6,7] These biases could have distorted the reported associations between smoking and dementia.[6,7] Thus, owing to the methodological limitations of case–control studies, there is a requirement for prospective studies to examine the association between smoking and dementia.

Some recent prospective cohort studies have suggested that smokers have an approximately 1.4-fold to 1.7-fold increased risk of dementia compared with individuals who have never smoked,[6,9–11] although other studies of this type have shown no such association.[6] The aim of the present nested case–control study was to investigate the association between cigarette smoking and the risk of disabling dementia using prospective data from members of a Japanese rural community.

MATERIALS AND METHODS

The study cohort was established in the town of Kyowa (Ibaraki Prefecture, Japan) in 1981 for community-based cardiovascular prevention program. The design of the cohort study has been described previously. [12,13] This cohort has been followed up with annual cardiovascular surveys, and surveillance for incidence and mortality of stroke and coronary heart disease. Within this cohort, elderly persons aged ≥65 years with disabling dementia, requiring for care were identified under the national long-term care insurance program, between April 1, 2000 and March 31, 2004. We did not have information on cognitive function prior to dementia. However, in order to reduce the potential effects of as yet undiagnosed dementia at the time of a given cardiovascular survey, the cohort included 6,343 men and women aged 35–85 years who participated in the surveys between 1981 and 1994 (of these, 4,085 subjects were over 65 years old between 2000 and 2004). Of these, 1,156 subjects were died, 252 subjects were moved out of study area before March 31, 2004. The overall participation rate was 70%. The Ethics Committee of the University of Tsukuba, Japan, approved the study procedures.

Long-term care insurance program for elderly aged ≥65

The details of the national long-term care insurance program for elderly aged ≥65 have been reported elsewhere.[14,15] In brief, the insurance program was started in Japan from April 2000. This program was essentially extended from the national health insurance system, and partially relied on subsides from general revenues from national, prefectures and municipalities. All individuals aged ≥40 are required to pay a supplement to their health insurance, which is transferred to the long-term care. The payment is directly withdrawn from their monthly income, shared with the employer or deducted from their public pensions. All

individuals are able to receive a long-term care through their resided municipals when they become 65 and older and also have disabling dementia and/or reduced activity of daily living.

Case-control analysis

Case selection

The cases were selected among the subjects aged >65 years between 2000 and 2004 who were regarded as suffering from dementia under the long-term insurance program. The dementia status were classified into six-ranks (0-V) and were reported by their primary care physicians according to the standardized physicians' manual issued by the Health and Welfare Bureau for the Elderly of Japan.[16] The dementia status were annually updated and were reviewed until they were withdrawn due to death or moving out of the study area. Individuals without dementia were classified as rank 0. Individuals who were diagnosed with mild cognitive dysfunction, but who had no dementia-related symptoms or behavioural disturbance and were capable of living independently, were classified as rank Ⅰ. Individuals who had moderate dementia-related behavioural disturbance and cognitive impairment with slight dependence were classified as rank Ⅱ. Individuals who had moderate-to-severe dementia-related behavioural disturbance and cognitive impairment with moderate dependence were classified as rank Ⅲ. Individuals who had severe dementia-related behavioural disturbance and cognitive impairment with heavy dependence were classified as rank Ⅳ. Finally, individuals with severe dementia-related behavioural disturbance and cognitive impairment who required medical treatment were classified as rank Ⅴ. Individuals who were ranked as Ⅱ or greater for the first time were regarded as cases in the present analysis. The validation for the cut-off point was examined by neuropsychiatrists through the subjects' cognitive functions (attention, memory, visuospatial function, language and reasoning) based on their ageing-associated cognitive decline (AACD), as defined by the International Psychogeriatric Association.[17] The

calculated sensitivity and specificity values from the validation study of 34 subjects were 36% and 90%, respectively.

History of stroke identification

The history of stroke was obtained from the annual cardiovascular surveys, surveillance for cardiovascular disease [13] from 1981 to the present, and/or statements from the primary care physicians. In present study, 85% of the stroke history was confirmed based on CT or MRI using standardized criteria. [18] The determination of stroke history without the imaging studies was conducted based on the clinical criteria.[19] Stroke was defined as rapid onset focal neurological disorder persisting for $\geq$ 24h, or until death. Transient ischemic attack was not included.

Control selection

We employed the risk-set sampling [20] of controls, i.e., matching randomly each case of dementia with two of all other individuals with no diagnosis of dementia in the study cohort who were alive and resided within the community on the date of diagnosis of dementia for the case and who had the same gender, year of given annual cardiovascular survey and age (± 2 years) as the case. The vital status of controls was assessed before the control selection.

Measurement of risk factors

Participants were interviewed smoking status (current, past, or never); those who smoked cigarettes were asked their age at start of smoking and the average daily number of cigarettes smoked at the time of a given annual cardiovascular survey. Those who had not smoked for 3 months or more were defined as past smokers. The past smokers were asked for their age at starting and quitting smoking, and the average daily number of cigarettes smoked. For each case, the latest measurements from a given survey between 1981 and 1994 were selected for the analysis. For controls, the measurements included in the analysis were selected from the same year of a given survey as the case.

The reliability of smoking questionnaire was tested in the same population. The proportion of upholding the same smoking status at 1 year after the time of a given survey between 1981 and 1994 (n=2314) was 97% for never-smokers, 87% for past smokers, 93% for current smokers (83% for smokers of <20 cigarettes per day, and 75% for smokers of >20 cigarettes per day).

Confounding variables included systolic blood pressure (mmHg), use of antihypertensive medication (yes and no), body mass index (BMI) (kg/ m^2), atrial fibrillation (Minnesota Codes 8-3-1 or 8-3-2), ST-T changes (Minnesota 4-1 to 4-3 or 5-1 to 5-3), ethanol intake (never-drinkers, ex-drinkers, or current drinkers), serum cholesterol (mmol/L), and diabetes mellitus (a fasting glucose level of >7.0 mmol/l, a non-fasting glucose level of >11.1 mmol/l, or the use of medication for diabetes).

Statistical Analysis

The paired Student's *t*-test was used to compare the values of baseline potential confounding factors and smoking status between incident cases and control subjects. The chi-square test was used to compare proportions of cases and control subjects. The odds ratios of total and subtypes of dementia were estimated according to the smoking status, tertiles of smoking years and tertiles of pack-years of smoking using the conditional logistic regression model. Adjustments for systolic blood pressure (mmHg), use of antihypertensive medication (yes *vs.* no), BMI (kg/m^2), alcohol intake (non-current drinkers *vs.* current drinkers), atrial fibrillation (yes *vs.* no), ST-T abnormalities (yes *vs.* no), serum total cholesterol (mmol/L), and diabetes mellitus (yes *vs.* no) were applied for multivariable analysis. A trend across the categories for smoking years and pack-years of smoking was conducted by assigning median values for each category. To examine effect modification, we conducted stratified analyses according to sex and use of antihypertensive medication (yes and no), and checked statistical interactions

by using cross-product terms of smoking status and stratifying variables. The presence of sex

interaction for the associations between smoking and risk of dementia was tested using

cross-product terms of smoking status and sex variables. All p-values for statistical tests were

two-tailed and values <0.05 were considered to reflect significant difference. All analyses

were conducted using the SAS statistical package version 8.2 (SAS Institute Inc., Cary, NC).

RESULTS

During 2000 to 2004, we identified 208 dementia cases, comprising 95 dementia cases with history of stroke and 113 dementia cases without such history.

Table 1 shows the risk characteristics of dementia cases and control subjects. The average age at the time of a given an annual cardiovascular survey and physical examination during 1981 to 1994 was 69 years for total and subtypes of dementia, and 68-69 years for controls. The proportion of men was 36% for total dementia, 43% for dementia with history of stroke, 30% for without such history, and 30 to 43% for controls. The proportions of current smokers were higher for total dementia for controls. The prevalence of hypertension, diabetes, and ST-T abnormalities was higher for total and subtypes of dementia than for controls. These case-control differences were more evident for dementia with history of stroke than for dementia without such history.

Table 2 shows age-, sex-, and survey-year-matched and multivariable adjusted odds ratios (95%CI) for total and subtypes of dementia according to smoking status. The multivariable odds ratios for current versus never-smokers were 2.3 (1.1-4.7) for total dementia, 2.4 (0.8-7.7) for dementia with history of stroke and 2.3 (0.9-6.0) for dementia without it. There was no significant excess risk among past smokers. We further analyzed the data by stratifying current smokers into two categories; <20 and ≥20 cigarettes/day and found a dose-response relationship for total dementia.

We also analyzed the data by stratifying past and current smokers into three categories according to the number of years of and the pack-years of smoking, and found a dose-response relationship with the number of years of smoking and risk of total dementia (p for trend = 0.04), but not with the pack-years of smoking (p for trend = 0.21) (Table3). The

dose-response relationship with the number of years of smoking was more pronounced for dementia with history of stroke although the excess risk did not reach statistical significance.

We examined for potential effect modification by stratifying the analyses for sex and use of antihypertesive medication (yes and no) (data not shown). There were no statistically significant interactions between smoking status and sex (p for interaction=0.43) or use of antihypertesive medication (p for interaction=0.80) for total dementia.

DISCUSSION

Our prospective study was the first to show that current smoking was associated with a two-fold increase in the risk of disabling dementia among Japanese. The association between smoking and risk of disabling dementia did not vary between persons with and without history of stroke. The Pooled European Studies of Dementia reported that current smokers had an increased risk of total dementia (relative risk [RR]=1.4; 95% confidence interval [CI]=1.0–1.9) and Alzheimer's disease (RR=1.7; 95% CI=1.2–2.5) compared with individuals who had never smoked.[9] Another prospective study of mixed ethnic groups (African-Americans, whites and Hispanics) in the USA reported that current smokers had an increased risk of Alzheimer's disease (RR=1.7; 95% CI=1.1–2.8) compared with those who had never smoked.[10] The Honolulu–Asia Ageing Study reported that current smokers had an increased risk of vascular dementia (odds ratio [OR]=1.7; 95% CI=1.0–2.9), but not for Alzheimer's disease, compared with those who had never smoked; however, this association was no longer significant after adjustment for cardiovascular and respiratory factors.[11]

A previous prospective study in Japan showed an association between smoking and increased risk of mortality from dementia.[21] That study followed 265,118 individuals aged ≥40 years over a period of 17 years, and documented 69 deaths from senile dementia with cerebrovascular lesions and 120 deaths from senile dementia without cerebrovascular lesions. The age-adjusted RR of senile dementia without cerebrovascular lesions for current smokers compared with never smokers was 1.6 (90% CI=1.1–2.4), but no association was found between dementia with cerebrovascular lesions. However, that study did not adjust for potential confounding variables including blood pressure levels, and the diagnosis of dementia was not validated because the diagnosis relied only on death certificates.

A previous study found that the higher pack-year exposure was associated with greater cognitive decline among current and former smokers. [22] We found no significant association between the pack-year exposure and risk of total dementia, either dementia with or without history of stroke. However, we found an association between the number of years of smoking and the risk of total dementia, which may suggest that a long-term exposure rather than a high dose of smoking may increase the risk.

Several mechanisms could account for the adverse effect of smoking on the risk of vascular dementia. Smoking causes arterio-atherosclerosis by directly injuring endothelial cells,[23] it reduces high-density lipoprotein cholesterol levels,[24] and it accelerates thrombus formation by increasing plasma fibrinogen [25] and platelet aggregability [26], decreasing fibrinolytic activities,[27] increasing hematocrit [28] and reducing blood flow in the brain due to vasoconstriction.[29]

Considering the association between smoking and Alzheimer's disease, a previous case–reference study showed that patients with this disorder and a history of smoking had lower regional cerebral blood flow in the temporal, parietal, occipital and frontal lobes bilaterally, compared with individuals who had never smoked.[30] When blood flow reaches a critical threshold of cerebral hypoperfusion, brain capillaries can be regionally damaged, and the normal release of nitric oxide and glucose, as well as oxygen delivery to the neurons, can be impaired.[31] These conditions can lead to cerebral metabolic dysfunction, which might contribute to the progression of neuronal degeneration.[32] Increased oxidative stress caused by smoking[33,34] is another potential cause of Alzheimer's disease through enhanced neurotoxcity.[35]

Nicotine, which is a major component of tobacco smoke, has a neuroprotective effect via a reduction of amyloid aggregation and neurotoxicity.[36] However, any potential beneficial

effect of nicotine is likely to be overwhelmed by the adverse effects of the other components of tobacco smoke.[33]

The strengths of our current study were its prospective design, and the comprehensive nature of cardiovascular surveys, which allowed that the association between smoking and risk of dementia is adjusted for important potential confounding variables. Moreover, because we used annual cardiovascular surveys that were carried out $\geq$ 5 years before the endpoint determination, severe dementia was unlikely to be present at the time of the risk-factor assessment. This would enhance our confidence that smoking behaviour was not influenced by subclinical dementia.

The major limitations of our study were as follows. First, there might have been a residual confounding effect on the association between smoking and risk of dementia. Although we adjusted for selected cardiovascular risk, we could not exclude the possible influence of unmeasured risk factors such as education level [37] and marital status.[38] Second, the misclassification for diagnosis of dementia was inevitable. The study had low sensitivity but high specificity for the diagnosis of disabling dementia. Thus, cases of disabling dementia were less likely to be contaminated by false-positive cases, but the false negative cases were likely to exist in the control pool. However, due to the low prevalence of disabling dementia (approximately 5-6% of persons aged $\geq$65), the contamination by false positive cases in the controls may be small. The controls could be contaminated by patients with mild cognitive impairments in the present study, which may attenuate the associations. Third, the smoking exposure could be misclassified due to self-reporting. However, previous studies showed reported that self-reported smoking was fairly reliable. [39, 40] In the present study, we examined answer-reanswer reliability with 1-year interval between 1981 and 1994 and found that the reliability for self-reported smoking status was high; 97% for never-smokers, 87% for past smokers, 93% for current smokers. Fourth, the smoking-dementia associations did not reach

statistical significance when we examined two subtypes of dementia, probably due to the low statistical power to detect the effects. Fifth, there was a long duration between the time at smoking status surveyed and the time at dementia diagnosed, i.e., 6 to 21 years, which would make interpretation for the results difficult. However, the results did not change materially when the analyses were conducted, stratified by the time duration 6-14 years (n=461) and 15-21 years (n=163). For example, odds ratios (95% CI) of total dementia in relation to current smokers were 1.8 (0.8-4.2) in the time duration of 6-14 years, and 2.0 (0.5-7.6) in the time duration of 15-21 years. There were no statistical interactions of two periods with smoking status, duration or the amount of smoking. Finally, we did not have imaging studies to confirm the subtypes of dementia, and dementia without a history of stroke did not necessarily correspond to Alzheimer's disease. However, the proportion of Alzheimer's disease among persons with dementia without history of stroke was 79% in a previous Japanese study,[41] suggesting that dementia without history of stroke in present study are likely to be Alzheimer's disease. In contrast, only 2% of persons with history of stroke were Alzheimer's disease in that study, suggesting that Alzheimer's disease cases were less likely to exist in cases of dementia with history of stoke.

In conclusion, our prospective study showed that smoking was associated with an increased risk of disabling dementia. The smoking-dementia association did not vary by stroke history. A dose–response relationship was observed between the duration of smoking and the risk, and a two-fold excess risk was found for smokers of $\geq$45 years in duration. Long-term cigarette smoking may raise the risk of disabling dementia.

ACKNOWLEDGMENTS

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Table 1.

Baseline characteristics of study population by case and control.

Table 2.

Odds ratios for dementia according to cigarette smoking status.

Table 3.

Odds ratios for dementia according to years of smoking and pack-years of smoking.

Table 1

	n	Age y	Men %	Systolic blood pressure mmHg	Use of antihypertensive medication %	BMI kg/m2	Alcohol Intake %	Current Smokers %	Serum Cholesterol mmol/L	Diabetes %	Atrial fibrillation %	ST-T abnormalities %
Total demenita												
cases	208	69.1	35.6	139.3*	34.0	23.3	24.0	22.6 *	5.33	9.8	1.9	9.6
control subjects	416	68.6	35.6	135.6	35.0	23.7	22.0	16.1	5.26	6.7	2.4	9.1
Dementia with history of stroke												
cases	95	69.4	42.1	142.2*	42.1	23.3	28.4	25.3	5.31	13.8 *	3.2	14.7**
control subjects	190	68.9	42.1	134.4	37.4	23.6	27.4	17.4	5.19	6.0	3.7	7.9
Dementia without history of stroke												
cases	113	68.9	30.1	137.0	27.4	23.2	20.2	20.4	5.34	6.6	0.9	5.4
control subjects	226	68.4	30.1	136.6	32.7	23.9	17.5	15.0	5.32	7.2	1.3	10.2

* $p < 0.05$ and ** $p < 0.10$ (difference between cases and controls)

Table 2

Smoking Status	Never	Past Smoker	Current Smoker	Current smoker, the number of cigarettes per day	
				< 20	≥ 20
Total dementia					
No. of cases	133	28	47	36	11
No. of control subjects	283	66	67	52	15
Age-,sex-, survey year-matched OR	1.0	1.4(0.6-2.8)	2.2(1.1-4.4)	2.1(1.1-4.3)	2.6(0.9-7.3)
Multivariable OR	1.0	1.5(0.7-3.3)	2.3(1.1-4.7)	2.2(1.1-4.7)	2.7(0.9-8.2)
Dementia with history of stroke					
No. of cases	56	15	24	19	5
No. of control subjects	120	37	33	26	7
Age-,sex-, survey year-matched OR	1.0	1.4(0.4-4.5)	2.4(0.8-7.1)	2.4(0.8-7.2)	2.5(0.5-11.9)
Multivariable OR	1.0	1.7(0.5-5.9)	2.4(0.8-7.7)	2.4(0.7-7.9)	2.5(0.4-14.4)
Dementia without history of stroke					
No. of cases	77	13	23	17	6
No. of control subjects	163	29	34	26	8
Age-,sex-, survey year-matched OR	1.0	1.3(0.5-3.5)	2.0(0.8-5.0)	2.0(0.8-4.9)	2.6(0.6-11.1)
Multivariable OR	1.0	1.5(0.6-4.3)	2.3(0.9-6.0)	2.2(0.8-5.9)	3.0(0.7-13.8)

Adjusted for body mass index, alcohol use, serum total choresterol, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, atrial fibrillation and ST-T abnormality.

Table 3

| Smoking Status | Never | Years of smoking | | | P for trend |
		0<years<34	34≤years<45	years≥45	
Total demenita					
No. of cases	133	23	22	30	
No. of control subjects	283	45	43	45	
Age-,sex-, survey year-matched OR	1.0	1.5(0.7-3.2)	1.8(0.8-4.3)	2.3(1.1-5.2)	0.04
Multivariable OR	1.0	1.7(0.8-3.7)	2.0(0.8-5.2)	2.3(1.0-5.4)	0.04
Dementia with history of stroke					
No. of cases	56	8	13	18	
No. of control subjects	120	21	25	24	
Age-,sex-, survey year-matched OR	1.0	1.3(0.4-4.2)	2.4(0.6-9.5)	3.4(1.0-12.1)	0.05
Multivariable OR	1.0	1.7(0.5-6.0)	2.7(0.5-13.2)	3.0(0.7-12.3)	0.13
Dementia without history of stroke					
No. of cases	77	15	9	12	
No. of control subjects	163	24	18	21	
Age-,sex-, survey year-matched OR	1.0	1.8(0.7-4.6)	1.5(0.5-4.9)	1.7(0.6-4.9)	0.29
Multivariable OR	1.0	2.0(0.7-5.7)	1.8(0.5-6.1)	1.8(0.6-5.7)	0.24

| Smoking Status | Never | Pack-years of smoking | | | P for trend |
		0<years<28	28≤years<46	years≥46	
Total demenita					
No. of cases	133	31	18	26	
No. of control subjects	283	47	42	44	
Age-,sex-, survey year-matched OR	1.0	1.9(1.0-3.8)	1.4(0.6-3.2)	2.0(0.8-4.5)	0.23
Multivariable OR	1.0	2.1(1.0-4.3)	1.3(0.5-3.3)	2.1(0.9-5.1)	0.21
Dementia with history of stroke					
No. of cases	56	15	10	14	
No. of control subjects	120	25	21	24	
Age-,sex-, survey year-matched OR	1.0	2.0(0.7-6.1)	1.7(0.5-6.2)	2.2(0.6-7.5)	0.36
Multivariable OR	1.0	2.5(0.8-8.1)	1.3(0.3-5.3)	2.2(0.5-8.5)	0.57
Dementia without history of stroke					
No. of cases	77	16	8	12	
No. of control subjects	163	22	21	20	
Age-,sex-, survey year-matched OR	1.0	1.9(0.8-4.6)	1.1(0.3-3.6)	1.7(0.5-5.8)	0.43
Multivariable OR	1.0	2.1(0.8-5.5)	1.0(0.3-3.8)	2.1(0.6-7.3)	0.33

Adjusted for body mass index, alcohol use, serum total choresterol, systolic blood pressure, use of antihypertensive medication, diabetes mellitus, atrial fibrillation and ST-T abnormality.