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Ⅲ．研究成果の刊行物別刷

Nicotine & Tobacco Research, Volume 12, Number 9 (September 2010) 944–949

Original Investigation

Cigarette smoking in middle age and a long-term risk of impaired activities of daily living: NIPPON DATA80

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Received December 21, 2009; accepted June 26, 2010

Abstract

Introduction: Few studies have reported the relationship between smoking in middle age and long-term risk of impaired activities of daily living (ADL).

Methods: We analyzed 2,276 men and women aged 47–59 years at the baseline survey of NIPPON DATA80 in 1980. At the follow-up survey in 1999, ADL was surveyed among 1890 survivors. Multivariate-adjusted odds ratio (*AOR*) and 95% *CI* of impaired ADL or of composite outcome of either death or impaired ADL according to baseline smoking status were calculated by multiple logistic regression analyses.

Results: In 1999, 386 participants were dead, and 75 participants had impaired ADL. Compared with nonsmokers, *AOR* (95% *CI*) of impaired ADL was significantly higher in current smokers at baseline (odds ratio [*OR*] 2.11 [1.09–4.06]). Compared with nonsmokers, *AOR* of impaired ADL was higher as the number of cigarettes increased (*OR* 2.04 [1.02–4.06] for <20 cigarettes/day and *OR* 2.35 [0.94–5.88] for >20 cigarettes/day; *p* for trend = .04). *AOR* of composite outcome for current smoking was 1.83 (1.37–2.41).

Discussion: Smoking in middle age would increase future risks of impaired ADL. Smoking cessation may be important to prevent future impairment of ADL as well as death.

Introduction

Numerous studies have reported that smoking is one of the major risk factors for cardiovascular diseases and cancer (Gandini et al., 2008; Shinton & Beevers, 1989; Ueshima et al., 2004; Wakai et al., 2006; Wolf, D'Agostino, Kannel, Bonita, & Belanger, 1988). On the other hand, cardiovascular diseases, especially stroke, were reported to be the main cause of impaired activities of daily living (ADL) in Japan (Hayakawa et al., 2000; Kamiyama et al., 1999). The associations between smoking and functional status decline including impaired ADL in the elderly have been previously reported (Ho, Woo, Yuen, Sham, & Chan, 1997; Kamiyama et al.; LaCroix, Guralnik, Berkman, Wallace, & Satterfield, 1993; Lammi, Kivela, Nissinen, Pekkanen, & Punsar, 1989; Parker, Thorslund, Lundberg, & Kareholt, 1996; Strandberg et al., 2008; Stuck et al., 1999; Sulander, Martelin, Rahkonen, Nissinen, & Uutela, 2005). Several follow-up study from western countries showed that smoking is a risk factor for functional status decline in elderly people (Ho et al.; LaCroix et al.; Lammi et al.; Parker et al.; Strandberg et al.; Stuck et al.; Sulander et al.). In Asia, where stroke mortality and morbidity are higher than western countries (Ueshima, 2007; World Health Organization [WHO], 2007), several studies reported the association between smoking and functional status in elderly people (Ho et al.; Kamiyama et al.). However, these studies were performed cross-sectionally or in short term and evaluated smoking status in old age. Therefore, the relation between smoking in middle age and long-term risk of impaired ADL in Asian countries has not been well investigated.

In Asian countries including Japan, the prevalence of cigarette smoking is higher than that in western countries, especially in men (Martiniuk et al., 2006). In 2005, the prevalence of smoking was 39.3% in Japanese men and 11.3% in Japanese women (Health and Welfare Statistics Association, 2007). In middle-aged Japanese men, the prevalence of smoking was higher,

doi: 10.1093/ntr/ntq121
Advance Access published on July 30, 2010

approximately 50%. Because the smoking rate is high in Japan and in other Asian countries, it is important to clarify the relationship between smoking and future risk of impaired ADL.

The purpose of this report was to examine whether smoking in middle age increases the risk of future impairment of ADL and composite outcome, including death. A 19-year follow-up study of representative Japanese samples from the National Survey on Circulatory Disorders of Japan was conducted to examine this question.

Methods

Participants and follow-up

Cohort studies of the National Survey on Circulatory Disorders of Japan comprise the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged (NIPPON DATA). The baseline survey of NIPPON DATA80 was performed in 1980. The detailed methods of this study have been described (Hozawa et al., 2009; Okamura et al., 2007; Ueshima et al., 2004). We analyzed the 19-year follow-up data from NIPPON DATA80 in this study.

In 1999, we asked 300 public health centers from all over Japan to participate in the follow-up ADL survey and 249 of them participated (Hozawa et al., 2009). In these areas, 2,724 men and women aged 47–59 years participated at baseline. Among these participants, we excluded 78 participants with a past history of coronary heart disease or stroke ($n = 34$) or missing information in the baseline survey ($n = 44$). We also excluded 83 participants who moved before the ADL survey. At follow-up, we surveyed 2,646 participants and information about ADL was collected. At follow-up, 386 participants had already died. Consequently, 86.8% ($n = 1,890$) of 2,177 remained survivors completed the ADL survey (Figure 1). Therefore, 1,890 participants were eligible for the analyses. Analyses were also done in 2,276 participants including 386 participants who were died before the ADL survey in 1999.

Detailed methods used to investigate ADL have been described (Hozawa et al., 2009; Nakamura et al., 2009). Briefly, participants were asked about five basic ADL-related items (feeding, dressing, bathing, toileting, and transfer [walking indoors]) modified from Katz, Downs, Cash, and Grotz (1970) and whether each of these could be accomplished without help, with partial help, or with full help. This survey was conducted through face-to-face interviews at home (83.2%), telephone interviews (10.5%), and other methods by physicians and public health nurses in public health centers in 1999. "Impaired ADL" was defined as partial or full support needed to perform any of the five basic ADL items. The composite outcome was defined as either all-cause death or impaired ADL. The Institutional Review Board of Shiga University of Medical Science (NO.12-18, 2000) approved the study.

Biochemical and physical examinations

Baseline blood pressure (BP) was measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated participants after at least 5 min of rest. Hypertension was defined as systolic/diastolic BP ≥ 140/90 mmHg or receiving antihypertensive medication. Body mass index (BMI) was calculated as weight divided by height squared (kilogram per square meter). Public health nurses obtained data including smoking behavior, as well as current health status and medical history. Smoking behavior was categorized as nonsmokers (including former smokers) and current smokers (light smokers [20 cigarettes/day or less] and heavy smokers [more than 20 cigarettes/day]). In 1980, nonfasting blood samples were separated by centrifugation within 60 min of collection and stored at −70 °C. Serum albumin and total cholesterol levels were measured using a sequential autoanalyzer (SMA12/60; Technicon, Tarrytown, NY) by bromocresol green staining for albumin and the Lieberman–Burchard direct method for total cholesterol at a specific laboratory (presently named Osaka Medical Center for Health Science and Promotion).

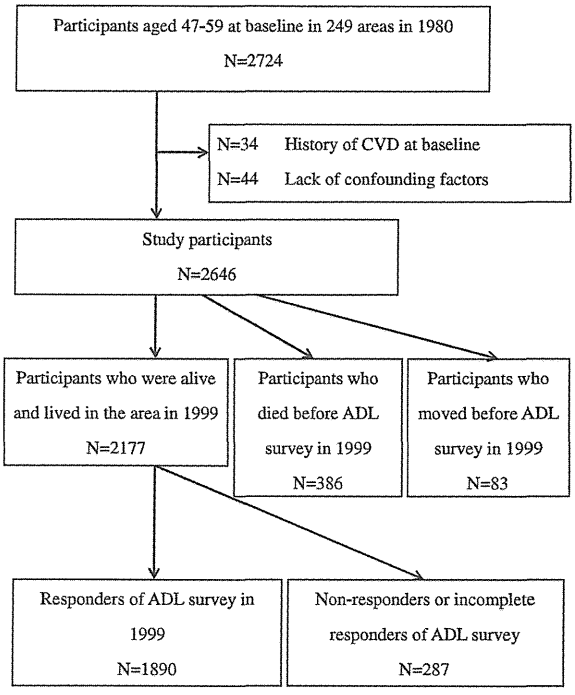

Figure 1. Flow chart of the study participants. N = numbers of participants; ADL = activities of daily living; CVD = cardiovascular diseases.

Statistical analysis

The relationship between smoking categories and impaired ADL or composite outcome of either death or impaired ADL was examined by multiple logistic regression analyses. The multivariate-adjusted odds ratio (*AOR*) and 95% *CI* for impaired ADL or a composite outcome was adjusted for age, gender, BMI (three categories: less than 18.5, 18.5–25, and 25 kg/m^2 and over), drinking (nondrinking and current drinking), BP (less than 120/80, 120–139/80–89, 140–159/90–99, and 160/100 mmHg and over or antihypertension medication), and serum total cholesterol and albumin levels. The nonsmoking group was set as the reference group. All analyses were performed by SAS 9.1 (Statistical Analysis System; SAS Institute, Cary, NC).

Table 1. Baseline characteristics of participants, NIPPON DATA80, 1,021 men and 1,255 women aged 47–59 years

	Men		Women	
	Nonsmoker[a]	Current smoker	Nonsmoker[a]	Current smoker
Number of participants (*N*)	340	681	1,161	94
Age (year)	52.8 ± 3.5	53.1 ± 3.5	53.2 ± 3.8	53.7 ± 3.8
BMI (kg/m²)	23.2 ± 2.9	22.3 ± 2.7	23.3 ± 3.4	22.8 ± 3.2
Serum albumin (g/dl)	4.42 ± 0.24	4.37 ± 0.26	4.37 ± 0.24	4.37 ± 0.22
Serum total cholesterol (mg/dl)	193.1 ± 32.9	184.4 ± 34.4	197.4 ± 32.9	198.7 ± 33.2
SBP (mmHg)	140.5 ± 20.4	140.1 ± 20.2	138.2 ± 20.5	132.3 ± 21.3
DBP (mmHg)	86.4 ± 12.2	84.5 ± 12.4	82.4 ± 11.3	79.3 ± 13.0
Prevalence of hypertension[b] (%)	57.1	55.8	50.3	39.4
More than 20 cigarettes/day (%)	–	39.4	–	6.4
Current drinking (%)	70.3	78.0	14.6	38.3

Note. Values are number, % or mean ± *SD*. BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure.
[a]Nonsmokers include former smokers.
[b]Hypertension was defined as SBP/DBP ≥ 140/90 mmHg or receiving antihypertensive medication.

Results

Baseline characteristics of participants are shown in Table 1. For men, current smokers had lower total cholesterol levels ($p < .001$) and lower BMI levels ($p < .001$) than nonsmokers. For both men and women, smokers had a higher prevalence of current drinking ($p < .01$) than nonsmokers.

At the ADL survey in 1999, 31 men and 44 women had impaired ADL. Table 2 shows the relationship between smoking categories and impaired ADL. The *OR* of impaired ADL in smokers was significantly higher than that in nonsmokers after multivariate adjustment (*OR* 2.11 [95% *CI*: 1.09–4.06]). The *OR*s were similar when analyzed for men and women separately (*OR* 2.23 [0.91–5.42] in men and 2.25 [0.81–6.24] in women).

Table 2. Relationship between baseline smoking status and impaired ADL assessed 19 years later, NIPPON DATA80, 1980–1999

	Nonsmoker	Current smoker	
Men and women combined ($n = 1,890$)			
Number of participants alive at the end of follow-up	1,314	576	
Number of participants who developed impaired ADL (%)	47 (3.6%)	28 (4.9%)	
Unadjusted *OR* (95% *CI*)	1	1.38 (0.85–2.22)	
Age and sex *AOR* (95% *CI*)	1	1.63 (0.87–3.05)	
Multivariate *AOR* (95% *CI*)[a]	1	2.11 (1.09–4.06)	
Men ($n = 778$)			
Number of participants alive at the end of follow-up	281	497	
Number of participants who developed impaired ADL (%)	8 (2.8%)	23 (4.6%)	
Unadjusted *OR* (95% *CI*)	1	1.66 (0.73–3.75)	
Age *AOR* (95% *CI*)	1	1.60 (0.71–3.65)	
Multivariate *AOR* (95% *CI*)[a]	1	2.23 (0.91–5.42)	
Women ($n = 1,112$)			
Number of participants alive at the end of follow-up	1,033	79	
Number of participants who developed impaired ADL (%)	39 (3.8%)	5 (6.3%)	
Unadjusted *OR* (95% *CI*)	1	1.72 (0.66–4.50)	
Age *AOR* (95% *CI*)	1	1.66 (0.63–4.36)	
Multivariate *AOR* (95% *CI*)[a]	1	2.25 (0.81–6.24)	
Men and women combined ($n = 1,890$)		<20 cigarettes/day	>20 cigarettes/day
Number of participants alive at the end of follow-up	1,314	383	193
Number of participants who developed impaired ADL (%)	47 (3.6%)	19 (5.0%)	9 (4.7%)
Unadjusted *OR* (95% *CI*)	1	1.41 (0.82–2.43)	1.32 (0.64–2.74)
Age and sex *AOR* (95% *CI*)	1	1.57 (0.81–3.06)	1.81 (0.75–4.41)
Multivariate *AOR* (95% *CI*)[a]	1	2.04 (1.02–4.06)	2.35 (0.94–5.88)

Note. ADL = activities of daily living; *OR* = odds ratio.
[a]Adjusted for age, gender, body mass index, drinking, blood pressure, serum total cholesterol and albumin levels.

Table 3. Relationship between baseline smoking status and composite outcomes (death or impaired ADL) assessed 19 years later, NIPPON DATA80, 1980–1999

	Nonsmoker	Current smoker	
Men and women combined (n = 2,276)			
Number of participants	1,501	775	
Number of composite outcomes	234 (15.6%)	227 (29.3%)	
Unadjusted *OR* (95% *CI*)	1	2.28 (1.85–2.80)	
Age and sex *AOR* (95% *CI*)	1	1.69 (1.29–2.22)	
Multivariate *AOR* (95% *CI*)[a]	1	1.83 (1.37–2.41)	
Men (n = 1,021)			
Number of participants	340	681	
Number of composite outcomes	67 (19.7%)	207 (30.4%)	
Unadjusted *OR* (95% *CI*)	1	1.78 (1.30–2.43)	
Age *AOR* (95% *CI*)	1	1.75 (1.28–2.41)	
Multivariate *AOR* (95% *CI*)[a]	1	1.84 (1.32–2.55)	
Women (n = 1,255)			
Number of participants	1,161	94	
Number of composite outcomes	167 (14.4%)	20 (21.3%)	
Unadjusted *OR* (95% *CI*)	1	1.60 (0.95–2.68)	
Age *AOR* (95% *CI*)	1	1.55 (0.91–2.62)	
Multivariate *AOR* (95% *CI*)[a]	1	1.82 (1.05–3.16)	
Men and women combined (n = 2,276)		<20 cigarettes/day	>20 cigarettes/day
Number of participants	1,501	499	276
Number of composite outcomes	234 (15.6%)	135 (27.1%)	92 (33.3%)
Unadjusted *OR* (95% *CI*)	1	2.03 (1.60–2.58)	2.78 (2.10–3.70)
Age and sex *AOR* (95% *CI*)	1	1.51 (1.13–2.02)	2.18 (1.54–3.10)
Multivariate *AOR* (95% *CI*)[a]	1	1.64 (1.21–2.21)	2.34 (1.64–3.33)

Note. ADL = activities of daily living; *OR* = odds ratio.

[a]Adjusted for age, gender, body mass index, drinking, blood pressure, serum total cholesterol, and albumin levels.

Compared with nonsmokers, the *AOR* of impaired ADL was higher with higher number of cigarettes (light smokers, *OR* 2.04 [1.02–4.06], and heavy smokers, *OR* 2.35 [0.94–5.88]; p for trend = .04).

Table 3 shows the relationship between smoking and composite outcome of impaired ADL or all-cause death. The multivariate *AOR* of composite outcome in current smokers was significantly higher than that in nonsmokers (*OR* 1.83 [1.37–2.41]). Results were similar in both men and women (*OR* 1.84 [1.32–2.55] in men and 1.82 [1.05–3.16] in women). Compared with nonsmokers, the *AOR* of composite outcome was higher with higher number of cigarettes (light smokers, *OR* 1.64 [1.21–2.21], and heavy smokers, *OR* 2.34 [1.64–3.33]; *p* for trend < .001).

Discussion

In this long-term follow-up study of a representative sample of the Japanese population, it was demonstrated that the risk of future impaired ADL was twice higher in smokers than that in nonsmokers in middle age. This trend was similar for composite outcome including all-cause death.

Several follow-up studies reported that smoking was related to future functional status decline (Ho et al., 1997; LaCroix et al., 1993; Lammi et al., 1989; Parker et al., 1996; Strandberg et al., 2008; Stuck et al., 1999; Sulander et al., 2005). However, most studies were from western countries and in short follow-up period. A recent study from Finland demonstrated the relationship between smoking habit in midlife and physical functional status in old age in a 26-year follow-up study (Strandberg et al.). These results from western countries are consistent with our results in Japan where the disease structure is different (Ueshima, 2007; WHO, 2007). In Asian countries, several studies reported a significant association between smoking in elderly and future functional status decline (Ho et al.; Kamiyama et al., 1999). Compared with these previous studies, our study covered a larger number of participants, had a longer follow-up period, and evaluated smoking status in younger age. Therefore, to our knowledge, this study is the first one to report the association between smoking in middle age and long-term risk of future impaired ADL in an Asian population.

A few studies have investigated the prevalence of impaired ADL in Asian countries. A survey by the Ministry of Health, Labour and Welfare of Japan reported that the prevalence of impaired ADL was 3.4% among elderly Japanese aged 65–74 years (The Research Group for Impaired Activity Daily Living and Quality of Life in the Elderly, 1997). Other studies in Japan and Singapore reported that the prevalence of impaired ADL among elderly was 6.4% and 6.6% (Konno et al., 2004; Ng, Niti, Chiam, & Kua, 2006); the prevalence was similar to that in our study (4.0%), which is relatively lower than that in western countries.

Our analysis on impaired ADL as the endpoint did not consider participants who were dead before ADL survey. Some of them might be impaired their ADL before death. Therefore, we analyzed the relation between smoking status and composite outcome (death or impaired ADL). In this analysis, we found that both results on the risk of impaired ADL and of composite outcome (death or impaired ADL) were similar. Nonsmokers would be able to live longer and to spend healthier life without impaired ADL than smokers.

A possible mechanism for the relationship between smoking and impaired ADL could be the occurrence of stroke (Hayakawa et al., 2000; Kamiyama et al., 1999) and chronic obstructive pulmonary disease (COPD; Garrod, Bestall, Paul, Wedzicha, & Jones, 2000; Lundback et al., 2003). Certainly, previous studies reported that smoking is a strong risk factor for stroke (Shinton & Beevers, 1989; Ueshima et al., 2004; Wolf et al., 1988) and COPD. Another mechanism by which smoking impairs ADL could be osteoporosis and occurrence of bone fracture (Katz et al., 1970). Osteoporosis was a major cause of bone fracture in older adults, and smoking was reported to be an important risk factor for osteoporosis (Wong, Christie, & Wark, 2007). The bone fracture in elderly due to smoking might be one mechanism for impaired ADL. We have previously reported that in our 1994 survey of NIPPON DATA80, 54% of impaired ADL was due to stroke in men and 22% in women. Also, 30% of impaired ADL was due to lower limb fracture in women (Hayakawa et al.). In the present study, 38.7% and 15.9% of male and female survivors with impaired ADL had self-reported history of stroke after baseline survey (data not shown). Stroke events caused by smoking would more strongly contribute to impaired ADL in Asian populations than in western populations.

This study has several limitations. First, we did not assess the baseline ADL conditions in 1980. However, it is unlikely that individuals with impaired ADL participated in the baseline survey because participants had to attend the local public health centers on foot without any assistance. Moreover, we did not consider the results of ADL survey in 1994 because the number of participants who had ADL data both in 1994 and in 1999 was not enough to analyze. Second, the category of nonsmokers includes former smokers because of the small sample size of the study. Therefore, the risk of impaired ADL among smokers may be underestimated. Third, we assessed ADL only in 1999. Some of participants who died before 1999 may have developed impaired ADL. Therefore, this analysis would have a potential impact of selection bias due to missing information of participants who died until ADL survey in 1999. Fourth, ADL assessment was conducted by face-to-face interviews for most of participants; however, other methods were used in 17% of participants.

In conclusion, our results suggest that smoking in middle age substantially increases the future risk of impaired ADL as well as composite outcome including death. Not only to prevent cardiovascular disease and cancer but also to prevent future disability, the importance of smoking cessation should be emphasized to smokers.

Funding

NT is supported by Japan Foundation for Aging and Health fellowship programs for young researcher. This work was supported by a Grant-in-Aid from the Ministry of Health and Welfare under the auspices of the Japanese Association for Cerebro-cardiovascular Disease Control, a Research Grant for Cardiovascular Diseases (7A-2) from the Ministry of Health, Labour and Welfare, and a Health and Labour Sciences Research Grant, Japan (Comprehensive Research on Aging and Health: H11-chouju-046, H14-chouju-003, H17-chouju-012, and H19-chouju-014). There was no role of the financial sponsors in the design, execution, analysis and interpretation of data, or writing of the study.

Declaration of Interests

None declared.

Acknowledgments

The authors thank all public health centers in Japan that cooperated with our study. The members of the NIPPON DATA80 Research Group are listed elsewhere (Hozawa et al., 2009).

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CVD Prevention and Control (2010) 5, 27–34

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γ-Glutamyltransferase and mortality risk from heart disease and stroke in Japanese men and women: NIPPON DATA90

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Received 18 February 2010; accepted 12 March 2010
Available online 24 April 2010

KEYWORDS
γ-Glutamyltransferase;
Heart disease;
Stroke;
Mortality;
Asia

Summary
Background: Studies have shown that baseline serum γ-glutamyltransferase (GGT) is independently associated with cardiovascular disease (CVD) risk in men and women. However, less is known whether GGT is similarly associated with both stroke and heart disease (HD) risk in Asia. We examined an association between serum GGT and deaths from stroke and HD in Japanese men and women.

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1875-4570/$ - see front matter
doi:10.1016/j.cvdpc.2010.03.003

Methods: From 1990 to 2005, we followed 7488 adults (3089 men) randomly selected from 300 districts throughout Japan, aged 30–95 with no history of coronary disease nor stroke at baseline. Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) according to sex-specific GGT strata.

Results: During the study period, observed deaths from HD and stroke were 165 (83 men), and 135 (66 men), respectively. After adjustment for confounding factors, HRs of HD death for 25th, 50th, 75th, and 90th GGT percentiles in reference to the lowest GGT stratum were 1.61, 2.28, 2.48, and 4.59 in women (P for trend = 0.001), and 0.90, 0.74, 1.42, and 1.56 in men (P for trend = 0.250). The corresponding HRs of total stroke death were 1.52, 0.95, 1.22, and 1.34 in women (P for trend = 0.785), and 0.75, 0.91, 1.26, and 1.02 in men (P for trend = 0.642). Results were similar when analysis was limited to never-drinkers.

Conclusion: This cohort study of representative Japanese men and women suggested that baseline GGT independently predicts future HD mortality risk, especially in women, but not stroke mortality risk in Asian.

Introduction

Elevated serum γ-glutamyltransferase (GGT) level has been shown to predict cardiovascular diseases (CVD) incidence [1,2] and mortality [3] but less is known whether GGT is independently associated with both heart disease (HD) and stroke mortalities. For example, a meta-analysis that pooled prospective cohorts showed that GGT was associated with both incident coronary heart disease (CHD) and incident stroke [4], but many of the enrolled studies [2,3,5,6] did not take into account effect of alcohol consumption. Furthermore, current evidence on association between GGT and CVD risk is largely based on US and/or European populations. Asian populations are far less studied for association of GGT with risk of HD and stroke [7]. Although we previously reported an independent association between GGT and CVD death [8], we felt that events were too few to study an association with HD and stroke separately. In this study with extended follow-up period, we investigated whether serum GGT level at baseline is independently associated with long-term mortality from HD and stroke in both men and women in Japan. The question is of particular importance because stroke is more common in Asia compared to Europe and US. In addition, mortalities from CHD and ischemic stroke were examined as our secondary outcomes. We studied a cohort of representative Japanese men and women that has been followed up for 15 years.

Methods

Study participants

The National Integrated Project for Prospective Observation of Non-communicable Disease and its Trends in the Aged (NIPPON DATA) consists of two ongoing cohorts that are based on two national surveys conducted in Japan. Detailed methods in constructing the cohorts were described elsewhere [9–11]. In brief, they were constructed upon the National Survey of Circulatory Disorder conducted in 1980, and in 1990, which become the bases of "NIPPON DATA80" [9] and "NIPPON DATA90" [10], respectively. Both surveys included physical examination, laboratory tests, and self-administered questionnaire on lifestyle and medical information. The present study was based only on NIPPON DATA90 because the baseline survey of NIPPON DATA80 did not contain measurement of serum GGT level.

We followed a total of 8383 community residents (3504 men and 4879 women; age 30 or older) from 300 randomly selected districts across the nation until November 15, 2005. The overall population of ⩾30-year-old in all the districts was 10,956, and the participation rate in the survey was 76.5%. Of the 8383 participants, we excluded 895 participants for the following reasons; no baseline GGT measurement (n = 662), those with CHD and/or stroke at baseline (n = 222), and with missing pertinent covariates (n = 11), leaving 7488 individuals for analysis (3089 men, 4399 women). We utilized the National Vital Statistics to ascertain the cause of death. In accordance with Japan's Family Registration Law, all death certificates, issued by a physician, are to be forwarded to the Ministry of Health, Labour and Welfare via the public health center in the area of residency. The cause of death is then coded for the National Vital Statistics. The 9th International Classification for Disease (ICD9) was used for deaths occurring up to the end of 1994, and the 10th International Classification for Disease (ICD10) for deaths occurring thereafter. Permission was obtained from the Management and Coordination Agency of the Japanese Government for use of pertinent information from the National Vital Statistics. The respective codes for ICD9 and 10 used were as follows: heart disease (HD), 393–429 (ICD9), I01–I09, I11, I13, I20–I50 (ICD10); stroke, 430–438 (ICD9), I60–I69 (ICD10); coronary heart disease (CHD), 410–414 (ICD9), I20–I25 (ICD10); ischemic stroke 433, 434, 437.8a, 437.8b (ICD9), I63, I69.3 (ICD10). The study was approved by the Institutional Review Board of Shiga University of Medical Science (No. 17–21, 2005).

Measurement

The baseline survey was conducted by a public health center in each area. Blood pressure was measured by a trained staff member using a standard mercury sphygmomanometer over the right arm of a seated participant after at least 5 min-rest. Body mass index (BMI) was calculated as weight in kilogram divided by square of height in meter. From the self-administered questionnaire, the following information

was obtained; physician-diagnosed diseases [Yes, No, Unknown] (stroke, myocardial infarction), status of clinical visit for the corresponding medical condition, and use of medication. Alcohol intake was first categorized into [Never, Current, Former], then further asked amount (''*go*'', the traditional Japanese unit for *sake*, per day; 1*gou* (180 mL) of *sake* contains 23 g of alcohol) of consumption for those who responded as ''current''. Based on these questions, we used three categories (never, past, current) in main analysis, and six categories (never, past, current <23 g of alcohol/day, current 23 g to <46 g/day, current 46 g to <69 g/day, and current ⩾69 g/day) in sensitivity analysis. Smoking status was categorized into three groups; never-smoker, ex-smoker, and current-smoker. Exercise status was grouped into three categories; ''unable to exercise due to a health related reason'', ''unable to exercise due to a non-health related reason'', and ''exercise regularly''. Public health nurses confirmed information on smoking, drinking habits, and medical history.

Non-fasting blood samples were obtained and serum was separated and centrifuged immediately after blood coagulation. Plasma samples were also obtained in a siliconized tube containing sodium fluoride. Serum GGT was measured using 3-carboxyl-4-nitroanilide substrate methods based on International Federation of Clinical Chemistry and Laboratory Medicine with Hitachi 736-60 (Hitachi Ltd., Tokyo, Japan). Glutamyl oxaloacetic transaminase (GOT; also known as aspartate aminotransferase, AST) and glutamyl pyruvic transaminase (GPT; also known as alanine aminotransferase, ALT) were measured using ultraviolet methods. Serum total cholesterol and triglycerides (TG) as well as plasma glucose were measured enzymatically. High-density lipoprotein (HDL) cholesterol was measured by the precipitation method using heparin-calcium. Lipid measurements were standardized using the Lipids Standardization Program from the Centers for Disease Control/National Heart, Lung and Blood Institute. Diabetes mellitus was defined as serum glucose ⩾200 mg/dL and/or presence of self-reported history. All samples were shipped to the central laboratory (SRL, Tokyo, Japan) for measurement.

Statistical analysis

Because the relationship between GGT and CVD mortality was different by gender in our previous study [8], all analyses were performed separately in men and women. For main analysis, GGT level was categorized into five groups using sex-specific cut-off points of the 25th, 50th, 75th, and 90th percentiles computed over the each gender group, following previous works by Lee and the colleagues [1,12,13]. In estimating mortality risk, we first calculated crude total mortality rates according to the GGT strata. Then, multivariate-adjusted hazard ratios (HRs) were estimated using Cox proportional hazards model. Because distributions for GOT, GPT, and TG were right-skewed, values were natural log-transformed (ln-GOT, ln-GPT, ln-TG) when entering models as well as upon calculating linear trend across baseline GGT strata. Model 1 was adjusted for age only. Model 2 was further adjusted for systolic blood pressure (mmHg), BMI (kg/m^2), smoking status, regular exercise status, and total and HDL cholesterol (mg/dL), ln-TG, and diabetes mellitus at baseline. In Model 3, we further adjusted for alcohol intake. Model 4 further included ln-GOT and ln-GPT. We conducted a parallel procedure on the subgroup who reported as a never-drinker. To avoid instability in estimation, we used 25th and 50th percentiles combined as a reference group for secondary outcomes (CHD, ischemic stroke) due to their fewer events. Trends across the GGT strata were tested by regression with a median value used for a corresponding GGT stratum. All the statistical tests were two-tailed, and values of $P < 0.05$ were considered significant. Statistical analyses were conducted with SAS release 9.1.3 (SAS Institute, Cary, NC, USA).

Results

Characteristics of the participants at baseline are shown in Table 1. Median age (years) at baseline was 51 for women and 52 for men. Median BMI (kg/m^2) was 22.5 for women and 22.9 for men. Only less than 7% of the women reported as a current-drinker whereas more than a half (59%) of the men did so. Majority (92%) of the women reported as a never-drinker. The 25th, 50th, 75th, and 90th percentile levels of GGT were 8, 12, 17, 26, and 52 U/L for women, and 15, 24, 41, 76, and 158 U/L for men. There was a clear gender difference in age distribution across GGT strata. As GGT level increased, the median age increased in women, whereas it decreased in men (P for trend < 0.001 for both). Despite such difference in age distribution, many cardiovascular risk factors were similarly associated with GGT level in both sexes; as GGT increases, BMI, total cholesterol, TG, systolic and diastolic blood pressure levels increased in both men and women (P for trend < 0.001 for all those variables in both sexes). The proportions of current-drinker and current-smoker were higher in higher GGT strata for both men and women, but there was a striking gender difference in absolute proportions such that both current-drinker and current-smoker were much fewer in women than in men even in the highest GGT group.

During the mean follow-up of 13.7 years, we observed 165 HD deaths (83 men), and 135 stroke deaths (66 men). Deaths due to CHD and ischemic stroke were 65 (40 men), and 83 (men 42), respectively. Estimated crude mortality rate, adjusted hazard ratios (HRs) for deaths from HD, CHD, total and ischemic stroke according to GGT strata are shown in Table 2 for women and in Table 3 for men.

In women, crude mortality rates (per 1000 person-years) were similar between HD and total stroke; 1.34, and 1.13, respectively (Table 2). By Cox regression models, we observed a significant graded positive association between GGT and HD mortality in women. After multivariate adjustment, the HRs of HD death of 25th, 50th, 75th, 90th GGT strata were 1.61, 2.28, 2.48, and 4.59 in reference to the lowest GGT group (Model 4, P for trend = 0.001). The association pattern of CHD death was similar to, and with apparently greater strength than HD (Table 2). In contrast, we observed no clear association between GGT and neither total stroke nor ischemic stroke death throughout the models.

In men, crude mortality rates (per 1000 person-years) were 2.00 for HD, and 1.59 for stroke, respectively (Table 3). In Models 3 and 4, we observed an apparent

J-shaped trend between GGT levels and HD death. The adjusted HRs for 25th, 50th, 75th, and 90th GGT percentiles in reference to the lowest GGT group were 0.90, 0.74, 1.42, and 1.56, respectively (Model 4, *P* for trend = 0.250). The J-shape association was more evident in CHD deaths with adjusted HRs for 50th, 75th, and 90th GGT percentiles being 0.47, 1.98, and 2.68. Similar to women, we observed no clear association between GGT and neither total nor ischemic stroke death throughout the models.

Table 1 Characteristics of the participants at baseline.

	Sex-specific GGT[a]					Total	
	<25th	25 to <50th	50 to <75th	75 to <90th	⩾90th		
Women							
No.	960	1138	1124	719	458	4399	
Age (years)	45	49	52	56	56	51	(41–62)
BMI (kg/m^2)	21.5	21.9	22.8	23.6	23.9	22.5	(20.5–24.8)
Total cholesterol (mg/dL)	192	200	206	214	220	203	(179–231)
HDL-C (mg/dL)	57	57	55	55	53	56	(46–66)
Triglycerides (mg/dL)	82	95	103	116	130	101	(71–145)
GOT (U/L)	18	19	20	22	27	20	(17–24)
GPT (U/L)	12	14	16	20	28	16	(12–22)
SBP (mmHg)	126	128	132	138	140	130	(118–146)
DBP (mmHg)	76	78	80	82	82	80	(70–88)
Use of antihypertensives (%)	12.5	16.0	21.4	29.1	31.2	20.3	
Diabetes mellitus (%)	2.1	3.0	3.7	6.5	7.9	4.1	
Smoking							
Never (%)	91.9	88.4	87.5	86.2	83.4	88.1	
Former (%)	1.9	3.6	2.5	2.1	2.4	2.6	
Current (%)	6.3	8.0	10.0	11.7	14.2	9.4	
Drinking							
Never (%)	96.7	93.7	92.1	90.4	84.1	92.4	
Former (%)	0.4	1.1	1.1	1.3	0.9	1.0	
Current (%)	2.9	5.2	6.9	8.3	15.1	6.7	
Regular exercise							
Not, for health (%)	5.8	6.0	6.0	8.3	9.4	6.7	
Not, for other reason (%)	78.1	74.3	75.6	71.8	71.8	74.8	
Yes (%)	16.0	19.7	18.3	19.9	18.8	18.5	
Men							
No.	681	831	795	472	310	3089	
Age (years)	56	55	51	49	49	52	(41–63)
BMI (kg/m^2)	21.4	22.4	23.4	24.2	24.0	22.9	(20.8–24.9)
Total cholesterol (mg/dL)	182	194	200	203	204	195	(174–221)
HDL-C (mg/dL)	48	48	48	47	51	48	(40–58)
Triglycerides (mg/dL)	93	108	132	154	172	119	(83–181)
GOT (U/L)	20	22	24	27	34	24	(19–29)
GPT (U/L)	16	19	24	31	42	22	(16–32)
SBP (mmHg)	132	132	136	140	138	136	(124–150)
DBP (mmHg)	80	80	84	88	88	84	(76–90)
Use of antihypertensives (%)	14.5	17.8	16.5	20.3	17.1	17.1	
Diabetes mellitus (%)	6.2	6.4	6.9	8.9	9.4	7.2	
Smoking							
Never (%)	26.3	21.8	20.0	17.4	12.6	20.7	
Former (%)	22.9	25.5	23.6	21.6	18.7	23.2	
Current (%)	50.8	52.7	56.4	61.0	68.7	56.1	
Drinking							
Never (%)	57.1	42.7	28.4	15.5	10.0	34.8	
Former (%)	6.8	8.2	5.9	4.7	3.5	6.3	
Current (%)	36.1	49.1	65.7	79.9	86.5	59.0	

Table 1 (*continued*)

	Sex-specific GGT[a]					Total
	<25th	25 to <50th	50 to <75th	75 to <90th	⩾90th	
Regular exercise						
Not, for health (%)	5.0	5.3	4.5	4.9	1.3	4.6
Not, for other reason (%)	71.2	72.0	72.8	75.8	76.8	73.1
Yes (%)	23.8	22.7	22.6	19.3	21.9	22.3

Values are expressed in median unless otherwise specified. Numbers in parenthesis are inter-quartile ranges.
Abbreviations: GGT, γ-glutamyltransferase; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; GOT, glutamyl oxaloacetic transaminase; GPT, glutamyl pyruvic transaminase; SBP, systolic blood pressure; and DBP, diastolic blood pressure.
[a] Cut-off GGT values (U/L) for 25th, 50th, 75th, and 90th percentile were 8, 12, 17, 26 and 52 in women and 15, 24, 41, 76 and 158 in men, respectively.

Table 2 Crude rates and multivariate-adjusted HR for heart disease and stroke deaths in women.

GGT category (value in U/L)	<25th (1–10)	25 to <50th (11–14)	50 to <75th (15–21)	75 to <90th (22–36)	⩾90th (37–385)	Total
Person-years	13,467	15,933	15,698	9844	6072	61,012
Heart disease death						
No.	10	16	21	19	16	82
Crude rate (per 1000 person-years)	0.74	1.00	1.34	1.93	2.64	1.34
						P for trend
Model 1	1	1.44	1.90	2.15	3.52	<0.001
Model 2	1	1.61	2.31	2.54	4.81	<0.001
Model 3	1	1.61	2.31	2.57	4.88	<0.001
Model 4	1	1.61	2.28	2.48	4.59	0.001
CHD death						
No.	5		7	7	6	25
Crude rate (per 1000 person-years)	0.17		0.45	0.71	0.99	0.41
						P for trend
Model 1	1		2.72	3.39	5.66	0.005
Model 2	1		3.27	4.40	7.95	0.001
Model 3	1		3.35	4.46	7.59	0.002
Model 4	1		3.56	5.01	10.31	0.002
Total stroke death						
No.	14	22	13	13	7	69
Crude rate (per 1000 person-years)	1.04	1.38	0.83	1.32	1.15	1.13
						P for trend
Model 1	1	1.40	0.84	1.06	1.10	0.890
Model 2	1	1.48	0.94	1.14	1.27	0.881
Model 3	1	1.50	0.93	1.15	1.32	0.819
Model 4	1	1.52	0.95	1.22	1.34	0.785
Ischemic stroke death						
No.	27		4	7	3	41
Crude rate (per 1000 person-years)	0.92		0.25	0.71	0.49	0.67
						P for trend
Model 1	1		0.30	0.64	0.57	0.298
Model 2	1		0.33	0.68	0.66	0.455
Model 3	1		0.32	0.67	0.69	0.483
Model 4	1		0.32	0.70	0.67	0.552

Model 1 was adjusted for age. Model 2 further included systolic blood pressure, BMI, smoking, exercise, total cholesterol, HDL-cholesterol, ln-TG, and diabetes mellitus. Model 3 further included alcohol intake (never, past, current). Model 4 further included ln-GOT and ln-GPT.
Abbreviations: CHD, coronary heart disease; GGT, γ-glutamyltransferase; BMI, body mass index; HDL, high-density lipoprotein; GOT, glutamyl oxaloacetic transaminase; GPT, glutamyl pyruvic transaminase; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

Table 3 Crude rates and multivariate-adjusted HR for heart disease and stroke deaths in men.

GGT category (value in U/L)	<25th (1–18)	25 to <50th (19–30)	50 to <75th (31–57)	75 to <90th (58–110)	⩾90th (111–1803)	Total
Person-years	8939	11,114	10,862	6488	4140	41,542
Heart disease death						
No.	30	24	14	10	5	83
Crude rate (per 1000 person-years)	3.36	2.16	1.29	1.54	1.21	2.00
						P for trend
Model 1	1	0.72	0.53	0.84	0.80	0.754
Model 2	1	0.81	0.62	1.02	1.08	0.704
Model 3	1	0.87	0.69	1.30	1.43	0.324
Model 4	1	0.90	0.74	1.42	1.56	0.250
CHD death						
No.	25		4	7	4	40
Crude rate (per 1000 person-years)	1.62		0.37	1.08	0.97	0.96
						P for trend
Model 1	1		0.38	1.39	1.49	0.343
Model 2	1		0.41	1.52	2.05	0.134
Model 3	1		0.46	1.97	2.74	0.048
Model 4	1		0.47	1.98	2.68	0.060
Total stroke death						
No.	20	16	16	10	4	66
Crude rate (per 1000 person-years)	2.24	1.44	1.47	1.54	0.97	1.59
						P for trend
Model 1	1	0.72	0.97	1.41	1.13	0.380
Model 2	1	0.76	0.96	1.35	1.16	0.440
Model 3	1	0.77	0.98	1.40	1.23	0.398
Model 4	1	0.75	0.91	1.26	1.02	0.642
Ischemic stroke death						
No.	24		13	4	1	42
Crude rate (per 1000 person-years)	1.20		1.20	0.62	0.24	1.01
						P for trend
Model 1	1		1.47	1.16	0.59	0.839
Model 2	1		1.45	0.97	0.52	0.616
Model 3	1		1.59	1.15	0.65	0.845
Model 4	1		1.64	1.19	0.65	0.794

Model 1 was adjusted for age. Model 2 further included systolic blood pressure, BMI, smoking, exercise, total cholesterol, HDL-cholesterol, ln-TG, and diabetes mellitus. Model 3 further included alcohol intake (never, past, current). Model 4 further included ln-GOT and ln-GPT.

Abbreviations: CHD, coronary heart disease; GGT, γ-glutamyltransferase; BMI, body mass index; HDL, high-density lipoprotein; GOT, glutamyl oxaloacetic transaminase; GPT, glutamyl pyruvic transaminase; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

The results were virtually unchanged when detailed categorization for alcohol intake was used in the models (data not shown). For subgroup analysis on never-drinker, observed number of death from HD and from stroke were 79 and 68 in women ($n = 4064$), and 41 and 24 in men ($n = 1074$), respectively. Estimated patterns of association were similar to the main analysis except that no J-shaped trend was observed between GGT and HD in men. The adjusted HRs for HD death of 25th, 50th, 75th, 90th GGT strata were 1.56, 2.36, 2.36, and 5.46 in women (P for trend < 0.001), 0.56, 0.79, 0.30, and 0.77 in men (P for trend = 0.564); the corresponding HRs for stroke death were 1.54, 0.98, 1.24, and 1.45 in women (P for trend = 0.679), 1.00, 0.70, 1.58, and 0.00 in men (P for trend = 0.815. No events in the highest group) (data not tabulated).

Discussion

In this 15-year follow-up study, we examined whether baseline GGT is independently associated with both HD and stroke deaths in Japanese men and women. We observed positive associations of GGT with the risk of total HD mortality and of CHD mortality in women. For men, there seemed to be a non-significant J-shaped trend of HD, especially CHD. In contrast, we did not observe a clear association between GGT and stroke mortality in either sexes.

Previous studies indicated that elevated GGT is associated with increased risk for CVD, but less is clear whether GGT is independently associated with both HD and stroke mortality. For example, Fraser and colleagues conducted a

meta-analysis pooling prospective cohorts, and showed that GGT was associated with both incident CHD and incident stroke [4]. However, many studies including those in the meta-analysis did not adjust for alcohol intake [2,3,5, 6,14], which left a possibility of confounding by alcohol effect. We dealt with this issue by both statistical adjustment and by restriction to never-drinkers, and the results from both approaches seemed similar. Another uncertainty is regarding a potential ethnic difference. Current evidence on association between GGT and CVD risk is largely based on US/European population, and Asians are far less studied. Since stroke is more common in east-Asia [15] compared to the US/European population, it is important to examine disease-specific association of GGT.

In our study population, stroke death rate was higher than that of CHD. Thus, it is unlikely that the observed null association with stroke risk is attributable to fewer deaths in light of positive association with CHD risk in women. However, the null association with stroke is not consistent with some studies including one from Japan that reported a positive association with incident stroke [7]. Although the exact reason for this inconsistency is unclear, we speculate followings reasons. First, stroke includes etiologically heterogenous conditions with different fatality risk [16,17]. Therefore, factors that affect stroke incidence may be different from those of stroke death. Second, prevalence of stroke subtype can be different between Asians and Caucasians [18], which could lead to difference in association.

We observed sex-difference in association of GGT with HD and CHD; not significant in men, whereas significant and monotonic in women. Similar sex-difference in association of GGT with incident stroke was reported from a Japanese population [7]. Such difference might be explained by the fact that GGT level is affected not only by alcohol consumption, but also obesity (through visceral and hepatic fat [19]), as well as smoking in the presence of alcohol [20]. Most women in our study were never-drinker, never-smoker, and young female tended to have lower BMI. In contrast, among our male group, both alcohol intake and smoking habit were common especially in the young who tended to have greater BMI. In a population such as our male group, the association of GGT may be obscured despite the attempt to deconfound. A larger sample size for never-drinking men is needed to examine this issue.

GGT has other potentially important determinants that can be even stronger than liver function or alcohol consumption [21]. Biological mechanism in explaining the link between elevated GGT and CVD mortalities is not fully understood. Serum GGT is considered to be a marker for insulin resistance [22], as well as for oxidative stress and inflammation which may lead to cardiovascular diseases [23,24]. Another mechanism has been suggested by histochemical analyses showing GGT activity expressed by macrophage-derived foam cells within human atheromas [25] co-localizing with oxidized LDL [26]. Furthermore, GGT is shown to mediate LDL oxidation [27], indicating that GGT is a potential marker for the preclinical atherosclerosis.

Major strengths of the study include prospective study design with longitudinal ascertainment of deaths, length of follow-up, and enrollment of both sexes with a broad age range based on the National Survey on randomly sampled areas nationwide, which made our cohort representative of the Japanese population. Several limitations should be mentioned. First, we did not have incidence data for CHD and stroke. Thus we were unable to examine potential difference between incidence and mortality. Second, we did not have information pertinent to hepatic conditions, such as chronic viral hepatitis, although we believe this limitation is less likely to distort our inference because our main outcomes are CVD mortalities, not hepatic/gastrointestinal or total mortalities.

Conclusion

We found that baseline GGT level was independently associated with long-term risk of HD mortality, especially in women, but not with stroke mortality in a representative sample of Japanese population.

Conflict of interest statement

None declared.

Role of funding source

This study was supported by a grant-in-aid from the Ministry of Health and Welfare under the auspices of the Japanese Association for Cerebro-Cardiovascular Disease Control, a Research Grant for Cardiovascular Diseases (7A-2) from the Ministry of Health, Labour and Welfare and a Health and Labour Sciences Research Grant, Japan (Comprehensive Research on Aging and Health: H11-Chouju-046, H14-Chouju-003, H17-Chouju-012, and H19-Chouju-014), and by the Korea Research Foundation Grant funded by the Korean Government (MEST) (KRF-2009-220-E00023). These sponsores had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Acknowledgments

The authors thank all members of Japanese Association of Public Health Center Directors and all staff members of the public health centers that cooperated with our study. Investigators and members of the research group are listed in Ref. [11].

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Takashima *et al. BMC Public Health* 2010, **10**:306
http://www.biomedcentral.com/1471-2458/10/306

BMC Public Health

RESEARCH ARTICLE Open Access

Population Attributable Fraction of Smoking and Metabolic Syndrome on Cardiovascular Disease Mortality in Japan: a 15-Year Follow Up of NIPPON DATA90

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Abstract

Background: Smoking and metabolic syndrome are known to be related to cardiovascular diseases (CVD) risk. In Asian countries, prevalence of obesity has increased and smoking rate in men is still high. We investigated the attribution of the combination of smoking and metabolic syndrome (or obesity) to excess CVD deaths in Japan.

Methods: A cohort of nationwide representative Japanese samples, a total of 6650 men and women aged 30-70 at baseline without history of CVD was followed for 15 years. Multivariate-adjusted hazard ratio for CVD death according to the combination of smoking status and metabolic syndrome (or obesity) was calculated using Cox proportional hazard model. Population attributable fraction (PAF) of CVD deaths was calculated using the hazard ratios.

Results: During the follow-up period, 87 men and 61 women died due to CVD. The PAF component of CVD deaths in non-obese smokers was 36.8% in men and 11.3% in women, which were higher than those in obese smokers (9.1% in men and 5.2% in women). The PAF component of CVD deaths in smokers without metabolic syndrome was 40.9% in men and 11.9% in women, which were also higher than those in smokers with metabolic syndrome (7.1% in men and 3.9% in women).

Conclusion: Our results indicated that a large proportion of excess CVD deaths was observed in smokers without metabolic syndrome or obesity, especially in men. These findings suggest that intervention targeting on smokers, irrespective of the presence of metabolic syndrome, is still important for the prevention of CVD in Asian countries.

Background

Obesity and clustering of its related factors, now called as metabolic syndrome, have been widely reported as important risk factors for cardiovascular diseases (CVD) [1-6], and, also in Asian countries including Japan, obesity has emerged as a new health problem [5]. The National Health and Nutrition Survey in Japan in 2005 showed that 22.4% of adult men and 10.8% of adult women were diagnosed as having metabolic syndrome [7]. Therefore, it is expected that metabolic syndrome or obesity would contribute to a large part of excess CVD events in Japan.

On the other hand, cigarette smoking is an established risk factor for CVD [8-12] and one of the biggest health problems in Asian countries including Japan [9,12,13]. In Asian countries, smoking rate in men is still high at 40 to 50% [14]. In Japan, smoking rate in 2005 was also high at 39.3% in men [15]. Therefore, smoking has largely contributed to increase CVD events in Asia, and it was reported that up to 30% of cardiovascular deaths was attributed by smoking in Asia Pacific region [16].

However, there have been few reports on the attribution of the combination of smoking status and metabolic syndrome (or obesity) to CVD deaths in Asian countries.

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