

Norwood, MA) for 48 h, and were cultured serum-free RPMI 1640 for overnight for using cell stimulation assays.

2.8. Real-time reverse transcription-polymerase chain reaction

Total RNA was extracted from cell extracts using a Qiagen RNeasy Micro Kit (Qiagen Inc.) following the manufacturer's instructions, and the abundance of specific mRNAs was determined by reverse-transcription (RT) and real-time quantitative polymerase chain reaction (PCR) analysis as described previously [11]. The sequences of the primers and probes for mouse Cat S are (forward) 5'-GTGGCCACTAAAGGGCCTG-3', (reverse) 5'-ACCGCTTTGTAGAAGAAGAAGGAG-3', and (probe) 5'-TCTGTGGCATCGACGCCAGC-3'; and Cat K are (forward) 5'-AGCAGGCTG-GAGACTAAGGT-3', (reverse) 5'-TTTGTGCATCTCAGTGGAAAGACT-3', and (probe) 5'-ACCTTCCCGAGCCCCTGTCTTCGTA-3'; glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was measured in parallel with genes of interest and used as an internal standard.

2.9. Elastase and collagenase assays

Differentiation of macrophage to foam cells were cultured in 24-well plates until confluent. After overnight starvation in FBS free Hanks's balanced salt solution (GIBCO), the cells were pre-treatment with or without apocynin (100 $\mu\text{mol/L}$, Sigma-Aldrich), or olmesartan (1 $\mu\text{mol/L}$), and then were cultured in the presence or absence of Ang II (0.1 $\mu\text{mol/L}$, Sigma-Aldrich) in serum-free medium containing either BODIPY[®] fluorescein-conjugated DQTM elastin from bovine neck ligament (300 $\mu\text{g/well}$, Molecular Probes, Eugene, OR) or water-insoluble nondenatured fluorescein-labeled collagen-type I (300 $\mu\text{g/well}$, Calbiochem, Darmstadt, Germany). After 24 h of incubation, culture media were analyzed for degraded elastin or collagen by Fluoroskan Ascent CF (Labsystems, Helsinki, Finland; excitation/emission: 485/530) [29]. To evaluate the role of Cat S, the reactions were also performed in presence or absence of a specific inhibitor of Cat S, morpholinerea-leucine-homophenylalanine-vinylsulfone-phenyl (LHVS, 5 $\mu\text{mol/L}$). Data were presented as relative units after adjustment for background levels. Data were representative of at least four independent experiments.

2.10. Statistical analysis

Data were shown as means \pm SD. Differences were analyzed by Student's *t*-test or by one-way analysis of variance with the *F*-test followed by Scheffe's multiple comparison test. A *P*-value of <0.05 was considered statistically significant.

3. Results

3.1. The effect of olmesartan on plaque morphology and cathepsins expression in brachiocephalic artery of apoE-deficient mice

Olmesartan at 3 mg/kg per day did not significantly affect arterial BP, HR, or body weight (control and olmesartan-treated apoE-deficient mice, mean arterial BP: 77.3 ± 5.4 mmHg and 73.0 ± 5.4 mmHg, HR: 597.4 ± 41.2 bpm and 616.5 ± 32.4 bpm, body weight: 25.8 ± 4.5 g and 26.1 ± 4.5 g, respectively; mean \pm SD, $n=8$). Olmesartan administration significantly decreased atherosclerotic lesion formation in the brachiocephalic artery of apoE-deficient mice after 8 weeks WD diet supplementation ($P<0.05$; Fig. 1A–C). In the histological analysis of the collagen by PSR-staining visualized with polarized light, significantly higher

collagen content was observed in olmesartan-treated mice compared with controls ($P<0.01$; Fig. 1D–F). In addition, the elastin levels determined by EVG-staining remained significantly higher in olmesartan-treated mice compared with control mice ($P<0.01$; Fig. 1G–I). Although the intense immunoreactivity of Cat S was observed in atherosclerotic lesions in the brachiocephalic artery in control mice, mainly in atheromatous plaque and in peripheral fibrous cap with weaker immunoreactivity than atheromatous plaque, the treatment with olmesartan significantly attenuated the Cat S immunostaining ($P<0.01$; Fig. 2A–C), whereas olmesartan administration did not affect the expression of Cat K (Fig. 2D–F). Double immunofluorescence staining in the brachiocephalic artery of apoE-deficient control mice demonstrated that Cat S colocalized with the macrophage marker Mac 3 in the shoulder region of the plaque, a vulnerable site of atherosclerotic plaque (Fig. 2G–I). In addition, colocalization of Cat K and Mac 3 was also detected in atherosclerotic plaque (Fig. 2J–L).

3.2. The effect of olmesartan on macrophage and smooth muscle cell accumulation in brachiocephalic atherosclerotic lesion of apoE-deficient mice

Extensive immunostaining of Mac 3 for macrophages in the intima of atherosclerotic plaque was detected in control apoE-deficient mice, while this Mac 3-positive area was significantly diminished by olmesartan administration ($P<0.05$, Fig. 3A–C). The immunoreactivity of ASMA was mainly observed in the media and intimal fibrous cap of atherosclerotic lesions (Fig. 3D). No significant difference in the intimal ASMA-positive area was observed between olmesartan-treated mice and control mice (Fig. 3E and F).

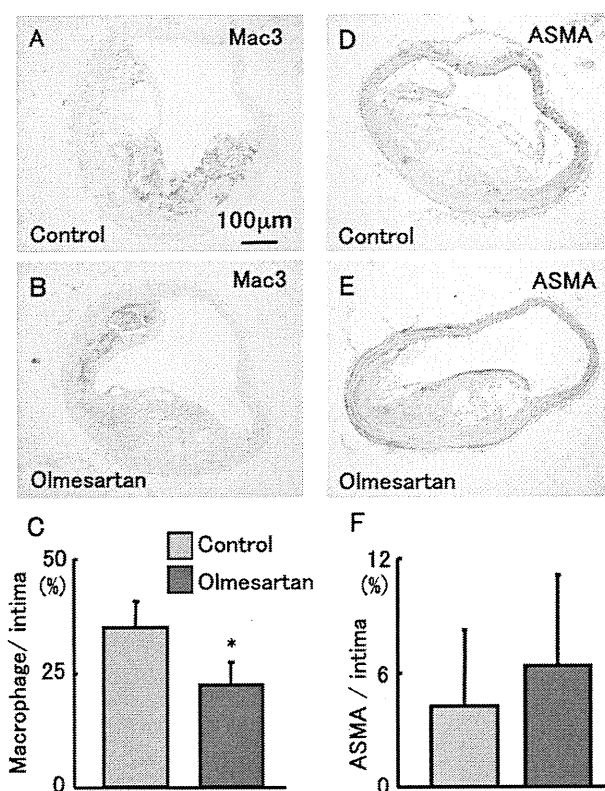


Fig. 3. Effect of olmesartan on macrophage (A–C) and smooth muscle cell accumulation (D–F) in the brachiocephalic artery of apoE-deficient control mice. Olmesartan administration significantly diminished the immunostaining area of Mac 3, but did not significantly affect the immunostaining area of ASMA. Values are means \pm SD, $n=8$. * $P<0.05$ versus control.

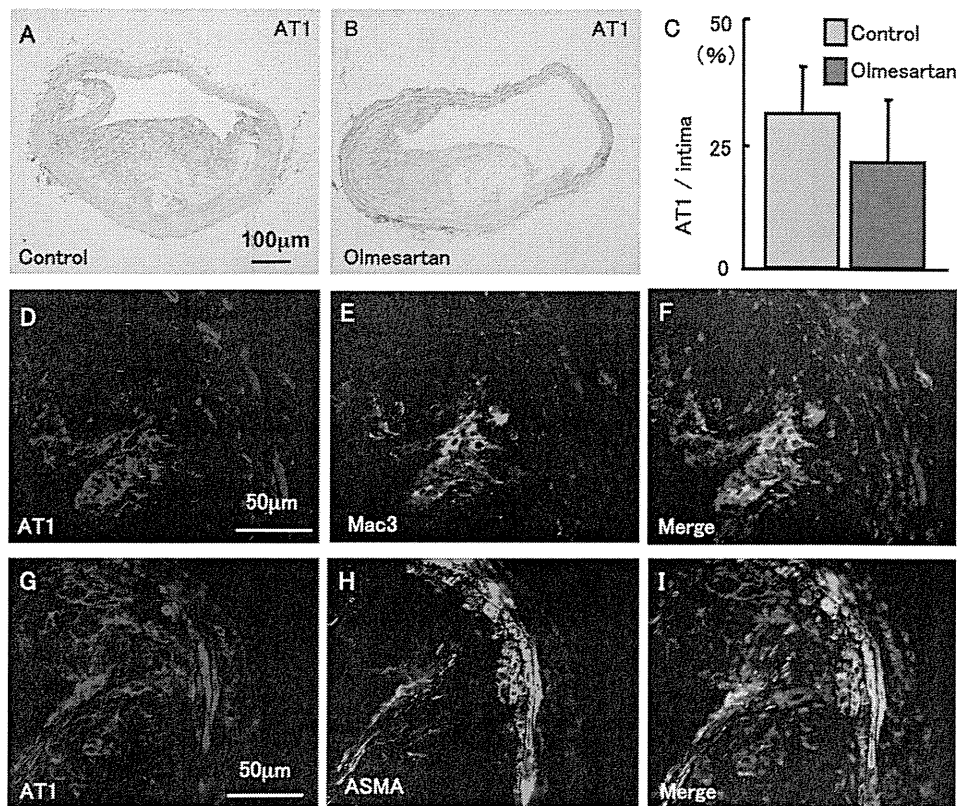


Fig. 4. Effect of olmesartan on the expression of AT1 receptor (A–C) in the brachiocephalic artery of apoE-deficient mice. Strong immunoreactivity of the AT1 receptor was observed in foam cells. Treatment with olmesartan did not significantly change the immunostaining of AT1 receptor. Values are means \pm SD, $n=8$. Double staining of AT1 receptor and macrophage (Mac 3; D–I) or smooth muscle cell actin (ASMA; J–L) in the brachiocephalic artery of apoE-deficient control mice. Colocalization of AT1 receptor and Mac 3 was detected in intimal lesions (I). Colocalization of AT1 receptor and ASMA was mainly observed in the fibrous cap and media (L).

3.3. Expression of AT1 receptor in brachiocephalic artery of apoE-deficient mice

Immunohistochemical analysis revealed that wide and intense AT1 immunostaining was observed at the intimal and medial regions (Fig. 4A and B). There is no significant difference in the AT1-positive area in atheromatous lesions between the control and olmesartan-treated groups (Fig. 4C). Double immunofluorescence of brachiocephalic artery sections with antibodies to the smooth muscle cell- or macrophage-specific markers and AT1 revealed that AT1 was localized both in smooth muscle cells and macrophages (Fig. 4D–F and H–J, respectively).

3.4. Regulation of Cat S and Cat K expression and activity in cultured macrophages

Real-time RT-PCR revealed that the amount of Cat S mRNA in cultured macrophages was increased by exposure to Ang II ($P<0.01$), and this effect was inhibited again by olmesartan and apocynin, a NADPH-oxidase inhibitor ($P<0.01$; Fig. 5A), whereas, no significant difference of Cat K mRNA was observed among these groups (Fig. 5B). Furthermore, Ang II enhanced macrophage-mediated collagenolytic and elastolytic activities ($P<0.01$), and these effects were inhibited by the administration of olmesartan ($P<0.01$), apocynin ($P<0.01$), and LHSV, a specific inhibitor of Cat S (collagenolytic activity: $P<0.05$, elastolytic activity: $P<0.01$; Fig. 5C and D).

4. Discussion

In this study, we demonstrated that treatment with AT1 antagonist olmesartan resulted in stabilization of atherosclerotic

plaque by higher levels of elastin and collagen in the plaque. Concomitantly, the expression of Cat S that is elastolytic and collagenolytic protease was suppressed in the intima by treatment with olmesartan. In addition, an in vitro experiment indicated that the expression of Cat S and elastolytic or collagenolytic activity induced by Ang II in cultured macrophages was attenuated by the administration of olmesartan. Furthermore, the accumulation of macrophages was inhibited by olmesartan administration. The colocalization of macrophages and Cat S was observed in atherosclerotic plaque. Taken together, our data suggest that Cat S derived from macrophages is involved in the mechanisms of atherosclerotic plaque vulnerability via ECM degradation, and that AT1 blocker maintained plaque stabilization through the suppression of both macrophage accumulation and the Cat S expression of macrophages.

In advanced atherosclerotic lesions, Ang II stimulates expression of MMPs [30–32], leading to destabilization of atherosclerotic plaque. Moreover, a previous report suggested that an AT1 receptor antagonist, irbesartan, contributes to plaque stabilization by the inhibition of MMPs in humans [24]. We also confirmed the high immunoreactivities of MMP-8 and MMP-9 in atherosclerotic lesions of WD-fed apoE-deficient mice, and the administration of olmesartan attenuated the expression of both MMP-8 and MMP-9 (data not shown). Moreover, these MMPs colocalized with the macrophage marker Mac 3 (data not shown). Therefore, the suppression of not only Cat S but also MMPs by olmesartan administration contributes to the maintenance of high levels of collagen and elastin in atherosclerotic plaque and helps to stabilize the plaque in apoE-deficient mice.

The treatment with olmesartan resulted in stable plaque in apoE-deficient mice in this study. Olmesartan administration was simultaneously commenced with WD feeding, therefore, it is sug-

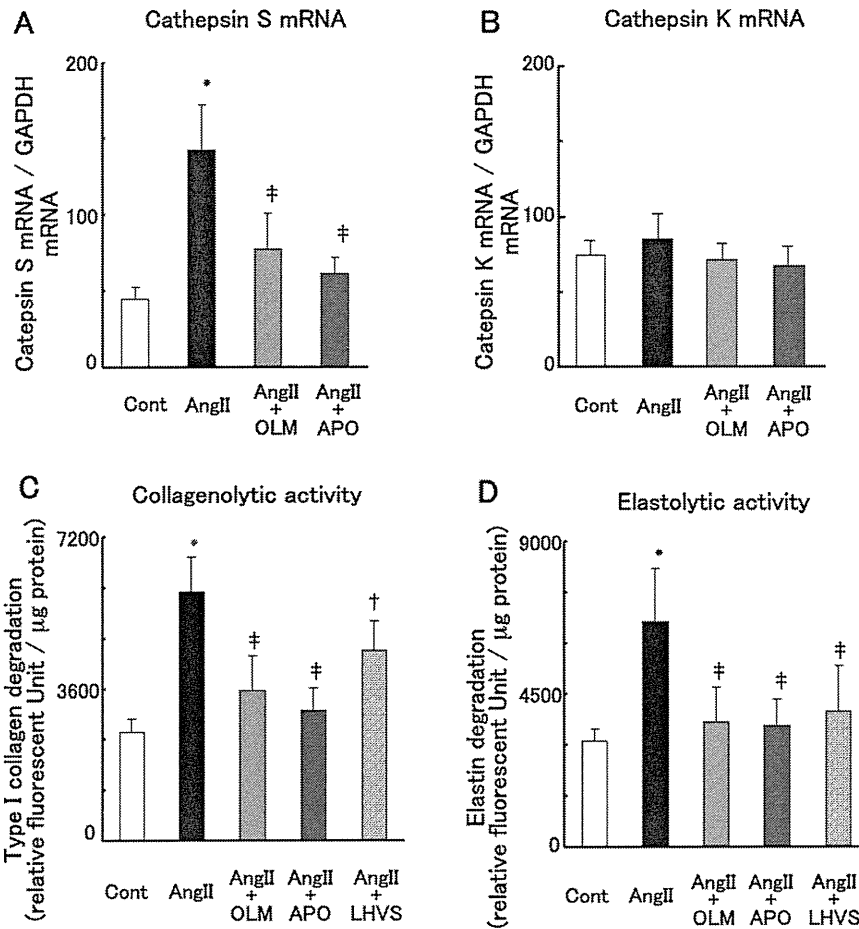


Fig. 5. Regulation of Cat S (A) and Cat K (B) expression and collagenolytic (C) and elastolytic (D) activity in cultured macrophages. Following pretreatment with olmesartan (OLM; 1 μ mol/L), apocynin (APO; 100 μ mol/L) and morpholinerea-leucine-homophenylalanine-vinylsulfone-phenyl (LHSV; 5 μ mol/L), respectively, for 30 min, the cells were cultured in the presence or absence of angiotensin II (Ang II; 0.1 μ mol/L) for 24 h. They were then subjected to quantitative real-time PCR analysis of Cat S (A) and Cat K (B) mRNA or to assay of collagenolytic activity (C) and elastolytic activity (D). Quantitative data are means \pm SD ($n=6$). * $P<0.01$ versus corresponding controls; † $P<0.05$, ‡ $P<0.01$ versus cells treated with Ang II alone.

gested that olmesartan might affect not only the matrix proteolysis in atherosclerotic plaque but also the plaque composition which was configured and altered at initiation and early-stage of plaque formation. Further investigations will be required to clarify these issues.

The mechanisms of olmesartan-induced Cat S suppression still remain unclear. Recently, Cheng et al. reported that AT1 receptor is involved in the activation of Cat S depending on the superoxide production during hypertensive myocardial remodeling [33]. It is well-known that the RA system contributes to superoxide production through NADPH-oxidase [28,34]; therefore, olmesartan may suppress Cat S levels via AT1 receptor-mediated superoxide production systems. Indeed, the expression of Cat S and the activity of extracellular matrix catabolism induced by Ang II in cultured macrophages were attenuated by the administration of apocynin, a NADPH-oxidase inhibitor. Furthermore, we observed the colocalization of the immunoreactivities of AT1 receptor and N(epsilon)-(hexanoyl)lysine (unpublished data), which is an oxidative stress biomarker [35,36]. On the other hand, daily administration of olmesartan did not affect BP, but maintained the high contents of collagen and elastin in atherosclerotic plaque, which were indices of plaque stabilization, in apoE-deficient mice in this study. This result supported the hypothesis that atherosclerotic plaque was stabilized not through BP suppression but through another pleiotropic effect of olmesartan. In our mouse model, we still have not determined whether the effect of olmesartan

on plaque stabilization is only mediated by the attenuation of free-radical-induced Cat S expression in macrophages. Further investigations will be required. Treatment of olmesartan had no effect on Cat K expression in atherosclerotic plaque. In cultured macrophages experiment, administration of olmesartan did not affect the levels of Cat K mRNA. From these results, it is suggested that AT1 receptor may not be involved in regulation of Cat K expression.

Previous reports revealed the expression of Cat S and Cat K in macrophages and smooth muscle cells in atherosclerotic plaque [10,12,37]. In the present study we also found that the strong expression of Cat S and AT1 was observed in intimal lesions. Immunofluorescent studies also showed the expression of AT1 on macrophages. Furthermore, the expression of Cat S and elastase activity in cultured macrophages was stimulated by treatment with Ang II. The elastolytic and collagenolytic activity induced by Ang II was inhibited by LHSV, a specific inhibitor of Cat S, suggesting a possible role for Cat S in Ang II-induced proteolysis of ECMs. Therefore, Cat S released from macrophages may participate in the mechanisms of atherosclerotic plaque vulnerability via catabolization of the ECMs including elastin and collagen. However, since the expression of Cat S and Cat K was detected in the fibrous cap of atherosclerotic plaque in our experiment, it is possible that Cat S and Cat K derived from smooth muscle cells may also be involved in the progression of atherosclerotic plaque vulnerability.

The immunoreactive Mac 3-positive area that was thought to be macrophage accumulation was significantly reduced in brachiocephalic atherosclerotic plaque of apoE-deficient mice by means of olmesartan administration. It has been reported that the AT1 antagonist irbesartan strongly decreased the levels of monocyte chemoattractant protein-1 mRNA and immunostaining in the lesion area, which are involved in macrophage infiltration into the lesion area [38]. In addition, Ang II upregulates the expression of adhesion molecules [39,40] thought to participate in monocyte accumulation in the vessel wall and to contribute to the development of atherosclerotic lesions. Therefore, olmesartan might suppress the accumulation of macrophages in plaque through the moderation of several chemokines and adhesion molecules as well as another AT1 antagonist.

Finally, the RA system and ECM proteases including cathepsins and MMPs may be greatly involved in the mechanisms of atherosclerotic plaque vulnerability, and inhibition of the RA system and these proteases by the AT1 antagonist might be beneficial in a treatment strategy for atherosclerosis and may stabilize plaques.

4.1. Perspectives

Our results demonstrated that treatment with olmesartan resulted in stabilization of atherosclerotic plaque alongside the suppression of Cat S and macrophage activities. Our findings support that an interventional treatment with olmesartan is expected to contribute to the inhibition of cardiovascular events. In future investigations, it will be of interest to elucidate the molecular mechanisms of the suppression of Cat S and macrophage activity by olmesartan.

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FACTORS ASSOCIATED WITH NONADHERENCE TO MEDICATION IN COMMUNITY-DWELLING DISABLED OLDER ADULTS IN JAPAN

To the Editor: Nonadherence to drug therapy is a serious problem for older people, because adherence to medication is essential for obtaining the optimal therapeutic effects of medication.^{1–4} Although numerous studies have identified the factors related to nonadherence to drug therapy, only limited studies have taken a wider perspective, focusing on adherence in older community-dwelling disabled adults and on factors affecting adherence.^{5,6} The aim of this study was to identify the factors associated with nonadherence to drug therapy in older community-dwelling disabled adults.

The present study used baseline data on participants in the Nagoya Longitudinal Study for Frail Elderly.^{4,7,8} The study population consisted of 1,722 older community-dwelling disabled adults (611 men, 1,161 women; mean age 80.3 ± 7.6 , range 65–104) and 1,502 caregivers (375 men, 1,127 women; mean age 64.1 ± 12.6 , range 31–93). The baseline data included the recipients' demographic characteristics, activities of daily living (ADLs), depressive symptoms as assessed using the short version of the Geriatric Depression Scale (GDS-15), physician-diagnosed chronic conditions, living arrangement, number of prescribed medications, and self-reported difficulty with self-medication management, which was assessed as previously described.⁴ The participants or family were also asked whether they were receiving any assistance for taking medication or medication management from others. The participants were divided into two groups: no difficulty with self-medication management, and difficulty with self-medication management. Data were also obtained from caregivers concerning their own personal demographic characteristics, their subjective health status, and burden as assessed according to the Zarit Burden Interview. The adherence rate to the prescribed medication was defined as the total number of pills taken divided by the total number of prescribed pills as assessed by the self-reported average medication adherence during 1 month. It was decided to use self-reporting rather than other forms of adherence measurements because they are prohibitively expensive and cumbersome, and there is little evidence that they are superior to self-report instruments.^{1,9} Nonadherence was defined as less than 80% of the adherence rate. Univariate and multivariate logistic regression were used to determine which characteristics of the disabled older adult or caregiver predicted nonadherence to prescribed medication.

Of 1,772 participants, 223 (12.6%) were categorized as nonadherent. Univariate logistic analysis demonstrated that participants living alone (vs living with someone, odds ratio (OR) = 1.43, 95% confidence interval (CI) = 1.04–1.96), with depression (GDS-15 ≥ 11 vs < 5 , OR = 1.61, 95% CI = 1.03–2.53), and with dementia (vs its absence, OR = 1.47, 95% CI = 1.10–1.96) and participants who had difficulty with self-medication management (vs no difficulty with self-medication, OR = 1.69, 95% CI = 1.24–2.30) were more likely to be nonadherent. Multivariate analysis (Table 1, Model 1) showed that medication nonadherence was associated with participants living alone, having depression, and having difficulty with self-medication. When participants who had difficulty with self-medication were divided as to the absence or presence of assistance (Model 2), nonadherence was associated with participants living alone, participants with depression, the presence of dementia, participants who had difficulty with self-medication but had no assistance, and participants with assistance. For participants who had difficulty with self-medication and had assistance, none of the variables of care recipients were associated with nonadherence in univariate analysis. Multivariate analysis revealed that a male caregiver and poor subjective health status of the caregiver were likely to result in nonadherence in participants having assistance.

In the present study, it was observed that participants who had difficulty with self-medication management had a high risk of nonadherence to medication. In particular, participants needing support but who did not have any, had a OR of nonadherence 3.2 times as high as those who had no difficulty with self-medication management, suggesting that medication management assessment is needed to determine which older people are at risk of medication management problems and to minimize adverse events attributable to poor medication adherence. Participants receiving medication management assistance had an OR of medication nonadherence 1.64 times as high as participants who had no difficulty with self-medication management. These results may imply that families or relatives living with disabled older patients may not always give appropriate assistance for medication management. A male caregiver and subjective poor health status of the caregiver were associated with recipient nonadherence to prescribed medication, suggesting that caregivers with those characteristics may tend to provide inadequate levels of assistance for medication or that neglectful behavior by caregivers may be involved in this association.

In conclusion, the results suggest that, in older community-dwelling disabled adults, the lack of medication assistance for those needing medication support was associated with a higher risk of nonadherence, although even those receiving assistance had a higher risk of nonadherence than those with no difficulty with self-medication management.

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Table 1. Logistic Regression Analysis for Nonadherence

Characteristic	Odds Ratio (95% Confidence Interval)		
	Multivariate*		
	Model 1 [†]	Model 2 [‡]	Multivariate for Those Having Assistance [§]
Care recipient characteristics			
Men (vs women)	0.86 (0.61–1.23)	0.89 (0.62–1.28)	—
Age (continuous variable)	0.99 (0.97–1.02)	0.99 (0.97–1.02)	—
Living alone (vs living with someone)	2.00 (1.35–2.95)	1.94 (1.31–2.86)	1.38 (0.59–3.25)
GDS-15 (range 0–15) (vs score 0–5)			
6–10	1.22 (0.85–1.77)	1.25 (0.86–1.81)	—
≥ 11	1.61 (1.02–2.53)	1.68 (1.06–2.66)	—
Presence of dementia (vs absence)	1.34 (0.91–1.97)	1.56 (1.04–2.36)	—
Medication management (vs self medication)			
Difficulty with self-medication	2.04 (1.37–3.05)	—	—
Absence of assistance	—	3.20 (1.92–5.34)	—
Presence of assistance	—	1.64 (1.05–2.54)	—
Caregiver characteristics			
Men (vs women)	—	—	1.90 (1.18–3.06)
Age (continuous variable)	—	—	1.00 (0.98–1.02)
Subjective health status (vs good to excellent)			
Fair	—	—	0.90 (0.54–1.49)
Poor	—	—	2.09 (1.11–3.94)

*The covariates included in the multivariate analysis were variables associated with nonadherence with $P < .05$ in univariate analysis. Activity of daily living score, presence of comorbid diseases (ischemic heart disease, congestive heart failure, cerebrovascular disease, diabetes mellitus, cancer, or hypertension), number of medication, and regular medical examination were not associated with nonadherence in univariate analysis. All analyses were performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL).

[†]Model 1 includes sex, age, living alone (vs living with someone), 15-item Geriatric Depression Scale (GDS-15) categories, presence of dementia (vs absence), and difficulty with self-medication (vs no difficulty).

[‡]Model 2 includes sex, age, living alone (vs living with someone), GDS-15 categories, presence of dementia (vs absence), and absence or presence of medication assistance (vs no difficulty).

[§]Logistic regression analysis was conducted to identify the predictor of the risk of nonadherence in 929 participants who had difficulty with self-medication and had assistance. The covariates included in the multivariate analysis were variables associated with nonadherence with $P < .05$ in univariate analysis. None of the variables of care recipients, including sex, age, comorbidity, depressive status, and number of prescribed medications, were associated with nonadherence in univariate analysis. The relationship to care recipient (spouse vs nonspouse) and the Zarit Burden Interview score were not associated with nonadherence in univariate analysis.

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL
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Factors influencing death at home in terminally ill cancer patients

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Aim: The purpose of this study is to investigate factors affecting terminally ill cancer patients dying at home.

Material: Ninety-two terminally ill cancer patients who were receiving home medical care services and died between April 2005 and December 2006 were included in the study. The data included patients' and caregivers' demographic characteristics, disease-related information, place of death, and status of home care support. To identify the factors predicting the place of death, multivariate logistic regression analyses were performed.

Results: Patients of families who had no preference regarding the place of death or a preference for death at home were more likely to die at home (vs preference for hospital death, odds ratio = 5.87, 95% confidence interval = 1.02–36.53; odds ratio = 90.35, 95% confidence interval = 8.15–1001.51, respectively) after adjusting for potential confounders. Meanwhile, if the patient's family preferred that the patient not die at home, the patient's place of death was not at his/her home irrespective of his/her preference.

Conclusion: The results suggested the stronger involvement of families' preferences regarding the patients' place of death over patients' own preferences. Therefore, factors affecting families' preferences need to be clarified for the dissemination of death at home for terminally ill cancer patients. *Geriatr Gerontol Int* 2010; 10: 154–160.

Keywords: death at home, factors, home medical care services, Japan, place of death, terminally ill cancer.

Introduction

For many years, various attempts have been made worldwide to provide optimal home care for terminally ill cancer patients who prefer to die at home.¹ However, according to the report on palliative care issued by the World Health Organization (WHO) in 2004, many of the patients who expressed their wishes of dying at home actually died in hospitals in Britain, the USA,

Germany, Switzerland and France.^{2–8} In Britain in particular, the proportion of patients who died at home has decreased from 27% in 1994 to 22% in 2003.^{9,10}

An opinion poll clarified that approximately two-thirds of Japanese patients diagnosed with the final stage of cancer preferred to receive medical treatments at home.¹¹ A similar trend is also observed in other countries.^{3,4,12–16} The Japanese Ministry of Health, Labor and Welfare initiated a Long-Term Care Insurance (LTCI) program in 2000,¹⁷ in which people requiring health care can receive home care services. In 2006, the services offered in this program were extended to terminally ill cancer patients. Moreover, with an aim to enhance home medical care, the designation of clinics supporting home care, which are required to provide round the clock home visiting medical care in

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cooperation with local home nursing stations was commenced. These series of movements toward the promotion of home care led to an emergence of group practice that only provides home visiting medical care without outpatient-based services. Despite an overt policy of the government to shift from institutional care to home care, the proportion of patients who died at home in Japan still remained approximately 12% in 2005, which is lower than that in Western countries,^{15,18,19} and even has a trend of gradual decline in recent years.

It is very natural for terminally ill cancer patients to wish to spend the last period of life in their own homes, where they can be themselves rather than being patients to receive care. However, many patients who wish to die at home are in fact hospitalized during the terminal stages and end up dying at the hospital. Other than patients' wishes of dying at home, there are other factors that may influence decisions as to whether or not patients can go home. Among the possible factors, conditions related to the patient's family or caregivers, by which patients' wishes themselves could be influenced, might be of particular significance. Also, environmental factors such as locations, accessibility to nearby home care clinics or hospitals if necessary, quality of the services provided and so on might have some influences on dying at home. Although several studies have investigated whether the places where patients die are the same as those where they wish to die, few studies have addressed the question of which factors can be requisites for terminally ill cancer patients to be able die at home if they wish.^{20,21} The purpose of this study is to investigate factors affecting terminally ill cancer patients to die at home, thereby to suggest possible rooms for improvement under the existing home care system in order to meet the needs of the patients.

Methods

Study design and subjects

This study consisted of a retrospective analysis of a total of 92 patients with a diagnosis of terminal stage cancer, who resided in Nagoya, an urban area of Japan with a population over 2 million, and had died between April 2005 and December 2006. All patients living at home were receiving various home care services through Mitsuba Home Care Clinic and from home visit nursing stations. The Mitsuba Home Care Clinic is a private clinic running a group practice of four full-time doctors specializing in offering home medical care on a round-the-clock basis within the city of Nagoya. All patients are assigned to one of the four doctors as an attending physician, who performs regular home visits. In case of emergency or upon patients' request, the clinic is prepared to offer irregular home visits by one of the four doctors on a shift. Informed consent for the

participation in this survey was obtained verbally from the patients and caregivers.

Data collection

The four doctors visited patients' homes and collected data from standardized interviews with patients or their surrogates, from caregivers and from visiting nurse records. The data, which were recorded on an electronic chart, included patients' and caregivers' demographic characteristics, the period between the doctor's first visit and the patient's death, living arrangements, the presence or absence of notification about diagnosis/prognosis of advanced malignancy to the patient, patient's or family's preference for the place of death, the primary caregiver's relationship to the patient, the presence or absence of other family caregivers to assist the primary family caregiver, administration of morphine, oxycodone or fentanyl, i.v. hyperalimentation, and number of home visits per week by the family physician or the home care nurse.

Analytical methods

To examine the differences between patients who died at home and at hospitals, the χ^2 -test or Student's *t*-test was used for independent variables or continuous variables, respectively. To identify the predictors for death at home, a logistic regression analysis was performed. Multivariate analysis was performed when a significant difference was observed in the univariate analysis. In the multivariate analysis, the following three models were employed: (i) model 1 that was designed based on patient characteristics; (ii) model 2 that was designed based on family characteristics; and (iii) model 3 that was designed based on the integration of models 1 and 2. The risk of a variable was expressed as an odds ratio (OR) with a corresponding 95% confidence interval (CI). The analysis was performed using the statistical software SPSS ver. 11.0.²² Probability values of 0.05 or less were considered statistically significant.

Results

Table 1 lists the characteristics of terminally ill cancer patients who died at home and at hospitals. Results of the χ^2 -test and Student's *t*-test revealed a significant difference in the following items: (i) whether the patient preferred to die at home; (ii) whether the patient's family preferred the patient to die at home; (iii) the frequency of home visits by the family physician; and (iv) the frequency of home visits by the home care nurse.

In order to identify the factors influencing the place of death of the patients, a logistic regression analysis was performed. As shown in Table 2, the unadjusted univariate analysis suggested that a higher probability of

Table 1 Characteristics of terminally ill cancer patients who died at home and hospital

Variable	No. of patients		<i>P</i> -value
	Death at home	Death at Hospital	
Patient demographics and clinical variables			
Age (mean \pm SD)	74.8 \pm 10.3	72.9 \pm 10.6	0.42
Sex (male/female)	29/31	18/14	0.68
Period between the doctor's first visit and the patient's death (days) (mean \pm SD)	49.5 \pm 52.5	69.7 \pm 82.7	0.26
Period (<27 days/ \geq 27 days between the first visit and death)	28/32	18/14	0.38
Type of cancer (gastrointestinal tract/lung/liver/gallbladder/pancreas/others)	25/10/9/16	11/8/6/7	0.71
Living with family (yes/no)	58/2	28/4	0.09
Notification of actual diagnosis/prognosis of advanced malignancy to the patient (yes/no)	39/21	14/18	0.50
Patient's preference for the place of death (hospital/neither of them/home)	5/22/33	13/15/4	<0.0001
Family caregiver's status and role			
Family's preference for the place of death (hospital/neither of them/home)	6/17/36	21/7/1	<0.0001
Primary caregiver's relationship to the patient (spouse/children/others)	26/27/6	14/12/3	0.75
Primary caregiver's sex (male/female)	9/50	10/19	0.04
Other family caregivers who assist the primary family caregiver (yes/no)	32/27	7/22	0.03
Health care system and support			
Administration of morphine, oxycodone or fentanyl (yes/no)	29/31	16/16	0.88
Administration of i.v. hyperalimantation (yes/no)	12/48	22/10	0.23
No. of home visits per week by the family physician (mean \pm SD)	3.4 \pm 1.8	2.6 \pm 2.2	0.64
No. of home visits per week by the home care nurse (mean \pm SD)	3.4 \pm 4.5	1.9 \pm 2.0	0.07
No. of home visits by the family physician (<2.6 times per week/ \geq 2.6 times)	24/36	22/10	0.01
No. of home visits by the home care nurse (<2.3 times per week/ \geq 2.3 times)	25/35	21/11	0.03

The Student's *t*-test was employed for continuous variables and the χ^2 -test was employed for independent variables. SD, standard deviation.

home death was associated with no preference regarding the place of death (vs preference for hospital death, OR = 5.72, 95% CI = 1.73–18.97), strong preference for home death (vs preference for hospital death, OR = 14.30, 95% CI = 3.25–62.93), no family preference regarding the patient's place of death (vs family preference for hospital death, OR = 8.50, 95% CI = 2.40–30.09), family preference for home death (vs family preference for hospital death, OR = 125.90, 95% CI = 14.18–1119.04), female caregivers (vs male caregivers, OR = 2.92, 95% CI = 1.03–8.31), presence of other family caregivers (vs absence of other family caregivers, OR = 3.73, 95% CI = 1.38–10.05), frequent home visits (average \geq 2.7/week by the family physician vs <2.7, OR = 3.30, 95% CI = 1.33–8.19), and frequent home visits (average \geq 2.4/week) by the home care nurse (vs <2.4, OR = 2.67, 95% CI = 1.10–6.53).

In the logistic regression analysis, when a significant difference was observed in the univariate analysis, a

multivariate analysis was performed using the three above-mentioned models. Using model 1, which was composed of patient characteristics, the following results were obtained. Patients with no preference regarding the place of death or a preference for home death were more likely to die at home (vs preference for hospital death, OR = 5.12, 95% CI = 1.37–19.14, OR = 16.53, 95% CI = 3.30–82.73, respectively). Using model 2, which focused on the characteristics of the family, we found that patients of families with no preference regarding the place of death or a preference for home death were more likely to die at home (vs family preference for hospital death, OR = 8.04, 95% CI = 2.08–31.08, OR = 136.57, 95% CI = 18.84–1347.51, respectively). The analysis of model 3, which was a combination of model 1 and model 2, found that the preference of the family was strongly associated with the place of death; patients of families with no preference regarding the place of death or a preference

Table 2 Logistic regression analysis of terminally ill cancer patients in connection with the place of death

Variable	Univariate	Multivariate		
	OR (95% CI)	Model 1 (patient) OR (95% CI)	Model 2 (family) OR (95% CI)	Model 3 (integration) OR (95% CI)
Patient's age (years)	1.00 (0.36–2.77)	1.02 (0.97–1.07)		1.00 (0.93–1.07)
Patient's sex (female, male = reference)	0.83 (0.35–1.97)	0.99 (0.35–2.84)		1.30 (0.24–6.93)
Period (≥ 27 days, <27 days = reference) [†]	1.47 (0.62–3.48)			
Type of cancer (gastrointestinal = reference)				
Lung	0.55 (0.17–1.77)			
Liver/gallbladder/ pancreas	0.66 (0.19–2.31)			
Others	1.01 (0.32–3.13)			
Stay with family (yes, no = reference)	4.14 (0.72–23.99)			
Notification to the patient (yes, no = reference) [‡]	0.73 (0.29–1.85)			
Patient's preference (hospital = reference) [§]				
Neither of them	5.72 (1.73–18.97)	5.12 (1.37–19.14)		2.18 (0.26–18.10)
Home	14.30 (3.25–62.93)	16.53 (3.30–82.73)		6.52 (0.79–53.66)
Family's preference (hospital = reference) [¶]				
Neither of them	8.50 (2.40–30.09)		8.04 (2.08–31.08)	5.87 (1.02–36.53)
Home	125.9 (14.2–1119.0)		136.6 (13.8–1347.5)	90.4 (8.2–1001.5)
Primary caregiver's sex (female, male = reference)	2.92 (1.03–8.31)		2.40 (0.47–12.27)	2.64 (0.34–20.21)
Caregiver's relationship (spouse = reference)				
children ^{**}	1.21 (0.47–3.10)		0.61 (0.15–2.54)	0.76 (0.12–4.81)
Others	1.08 (0.23–4.98)		1.50 (0.20–11.07)	1.44 (0.16–12.97)
Other family caregiver (presence, absence = reference)	3.73 (1.38–10.05)		3.03 (0.79–11.68)	2.87 (0.66–12.47)
Narcotic drugs (yes, no = reference) ^{††}	0.94 (0.39–2.21)			
Intravenous hyperlimentation (yes, no = reference) ^{‡‡}	0.55 (0.21–1.46)			
Family physician visit (≥ 2.6 times, <2.6 = reference) ^{§§}	3.30 (1.33–8.19)	2.23 (0.79–6.26)		1.36 (0.33–5.61)
Home care nurse visit (≥ 2.3 times, <2.3 = reference) ^{¶¶}	2.67 (1.10–6.53)	2.78 (0.97–7.91)		1.19 (0.26–5.57)

[†]The period between the doctor's first visit and the patient's death (days). [‡]Notification of actual diagnosis/prognosis of advanced malignancy to the patient. [§]Patient's preference for the place of death. [¶]Family's preference for the place of death. ^{**}Other family caregivers who assist the primary family caregiver. ^{††}Administration of morphine, oxycodone, or fentanyl. ^{‡‡}Administration of i.v. hyperalimination. ^{§§}No. of home visits per week by the family physician. ^{¶¶}No. of home visits per week by the home care nurse. CI, confidence interval; OR, odds ratio.

for home death were more likely to die at home (vs preference for hospital death, OR = 5.87, 95% CI = 1.02–36.53, OR = 90.35, 95% CI = 8.15–1001.51, respectively) after adjusting for potential confounders.

Next, logistic regression analyses were performed after excluding the variables that were strongly associated with home death, patient and family preference for place of death. As shown in Table 3, model 1 and model

Table 3 Logistic regression analysis of terminally ill cancer patients in connection with the place of death

Variable	Multivariate		
	Model 1 (patient) OR (95% CI)	Model 2 (family) OR (95% CI)	Model 3 (integration) OR (95% CI)
Patient age (years)	1.01 (0.96–1.06)		0.97 (0.94–1.06)
Patient sex (female, male = reference)	0.96 (0.37–2.47)		1.24 (0.35–4.34)
Primary caregiver's sex (female, male = reference)	2.03 (0.67–6.11)	1.82 (0.50–6.61)	
Caregiver's relationship to the patient (spouse = reference)			
Children [†]		1.28 (0.43–3.87)	1.26 (0.33–4.83)
Others		0.80 (0.24–2.67)	0.74 (0.18–3.04)
Other family caregiver (presence, absence = reference)	3.72 (1.15–9.29)	3.09 (1.02–9.32)	
Family physician (≥ 2.6 times, < 2.6 = reference) [‡]	2.83 (1.09–7.31)		2.70 (0.95–7.70)
Home care nurse (≥ 2.3 times, < 2.3 = reference) [§]	2.25 (0.88–5.74)		2.13 (0.74–6.12)

[†]Other family caregivers who assist the primary family caregiver. [‡]No. of home visits per week by the family physician. [§]No. of home visits per week by the home care nurse. CI, confidence interval; OR, odds ratio.

2 identified frequent home visits by the family physician and the presence of other family caregivers as the variables associated with home death. The full adjustment in model 3 demonstrated that patients who had other family caregivers were more likely to die at home (OR = 3.09, 95% CI = 1.02–9.32).

Discussion

Analysis of the results

The ratio of deaths at home obtained in this study was 65% higher than that obtained in a previous study.²⁹ The higher rate of death at home in the present study may be due to the fact that the data was collected in a practice that only provides home care. In this study, various factors that affect the place of death were clarified by analyzing the data collected from a single home care clinic located in an urban area. We observed that among the patients who died at home, those who lived with family caregivers and had very frequent home visits by the family physician were greater in number than those who lived without family caregivers and had fewer visits by the family physician. This suggests that the place of death is not simply determined by the patient's and/or family's wishes but can be determined by other factors such as social background or service provisions for home care. Regarding the influence of preference on the place of death, our results suggest stronger influence of the family's preferences over the patient's own preferences. However, there is a possibility that the patient's own preferences themselves might be influenced by the family's preferences if the priority of the patient's wish is thought not to cause any nuisance to his/her family. Although the factors associated with the patient's and the family's wish regarding the place of death were so influential that they may relatively weaken the influences of other factors, their wish might also be deter-

mined by many other confounding factors as suggested. Therefore, we performed a logistic regression analysis, excluding the patients' and families' preferences regarding the place of death. The result of the logistic regression analysis demonstrated that frequent visits by family physicians and the existence of other family caregivers appear to be significantly associated with patients' death at home relative to frequent visits by home care nurses. What this result implies is that more patients may be able to fulfill their wishes of dying at home if frequent on-demand visits by family physicians with support from complementary family caregivers are available. Whilst almost all home care nursing services are provided by a group, which enables them to provide round-the-clock visiting services, the majority of family practitioners in Japan maintain solo practices, which makes it difficult for them to provide such seamless home medical care and meet patients' needs. Although many home care medical services are provided in cooperation with home care nursing services, most of which are able to receive calls anytime or visit patients' homes whenever necessary, there still exists obstacles for the implementation of seamless cooperation partly because they are in many cases operated by different running bodies. In order to respond well to patients' needs as suggested from the present results, much improvement in the quality of service provisions is urgently required.

Comparison with other studies

In a previous systematic review, 17 factors were identified as influencing the place of death in terminally ill cancer patients.²³ The following factors were associated with a lesser probability of death at home: (i) non-solid cancers such as leukemia and myeloma; (ii) being of an ethnic minority; (iii) availability of beds in hospitals; (iv) residence in an area with easy accessibility to medical treatment; and (v) previous hospitalization. On the

contrary, the following factors were associated with a higher probability of death at home: (i) a long clinical history; (ii) a decrease in physical function; (iii) excellent social circumstances; (iv) a patient's preference to die at home; (v) a family's strong preference that the patient die at home; (vi) use of visiting care services; (vii) use of visiting care services available 24 h in case of emergency; (viii) residence in rural areas; (ix) staying with relatives; (x) receiving family support; (xi) being married; and (xii) a tradition of home being the place of death. Another study suggested the importance of caregivers' satisfaction with home medical care for patients to be able to die at home.²⁴

Many of the patients who participated in this study died at home despite the fact that they were urban residents who had relatively easier access to hospitals in case of emergency. Likewise, the convenience of what the patients and their families had benefited from by easy access to home medical care services provided by an urban-based group practice may lie behind the higher rate of death at home observed in the present study. Among the patients who died at home, none of them had non-solid cancer such as leukemia and myeloma, which is in keeping with a previous report.²⁵⁻²⁸ In the present study, the following factors were associated with a higher probability of death at home^{23,25}: (i) patient's wish; (ii) family's wish; (iii) use of visiting care services; (iv) use of visiting care services available 24 h in case of emergency; and (v) staying with relatives. However, unlike previous studies,^{23,26-28} the association of these factors with death at home did not persist except for the family's wish in the multivariate analysis.

Limitations of study and future directions

The data used in this study were collected from a single clinic with a group practice providing only home care. Although such a type of practice is recently emerging due to increased demand, particularly in urban areas, it is not yet a common type of medical practice overall. Therefore, the results obtained cannot necessarily be generalized in other clinical settings given the uniqueness of services this clinic was able to offer. Because the information obtained in this study relied largely upon the interviews of patients or their family caregivers made by the physicians who were directly engaged in the care provided, data related to the responses of the interviewees can be biased, given possible considerations of the respondents to not offend their attending physicians. Also, the low rate of notification of diagnosis/prognosis to the patients can raise a question about the validity regarding what the patients had expressed as their true preferences. Other than the variables we adopted in this study, there was a lot of other information that we did not collect such as patients' activities of daily living, physical symptoms, mental status, com-

petence to express themselves, relationship to nurses/doctors, social environment and caregivers' age and health condition^{23,26,28} which might have influenced the results. In the present study, the possible change in the family's preference regarding the place of the patient's death from the first visit until the patient's death was not addressed.

It is desirable for a patient to die at a place of his/her preference. However, the present situation surrounding home care service provisions does not necessarily fulfill patients' wishes of dying at home if they do not exist. The results of the present study suggest a strong involvement of family preference in the very important decision-making process related to patient's autonomy. Under the current family environment where only a limited source of informal care can be expected, the significance of improving home care services in order for patients to be able to die at home was confirmed in this study. Further investigations to clarify factors that would determine or influence family preference in choosing place of death for the patient are strongly desired.

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〈原 著〉

在宅療養要介護高齢者の介護環境ならびに生命予後，入院， 介護施設入所リスクの性差

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要約 目的：要介護認定を受けた在宅療養中の高齢者の性別による身体機能，疾病背景，介護環境（生活環境，介護者の有無ならびに続柄，サービス使用状況），さらに3年間の生命予後，入院，施設入所の相異を明らかにする。**方法：**名古屋市在住で要介護認定を受け在宅療養中の高齢者1,875名，さらにその主介護者1,568名を対象にした縦断調査（the Nagoya Longitudinal Study for Frail Elderly）の登録時のデータならびに3年間の死亡，入院，介護施設への入所に関する縦断的データを使用した。**結果：**登録された要介護者の性別構成は女性（66.3%）が男性（33.7%）の約2倍存在していた。男性に比較して女性要介護高齢者の平均年齢は高く（女性：81.5±7.5（SD）歳，男性：78.8±7.6（SD）歳， $p<0.001$ ），独居が多く（女性：26.2%，男性：14.6%， $p<0.001$ ），主介護者が配偶者である割合が男性要介護高齢者に比較して低かった（女性：22.1%，男性：73.6%， $p<0.001$ ）。女性要介護高齢者は訪問介護サービスの利用率が高く（女性：48.8%，男性：43.2%， $p=0.021$ ），また重篤な併存症の有病率は男性に比較して低く（男性 vs 女性，脳血管疾患：46.6% vs 28.3%， <0.001 ；慢性閉塞性肺疾患：9.9% vs 5.9%， $p=0.003$ ；悪性腫瘍：12.9% vs 7.3%， $p<0.001$ ），骨折の罹患率（過去5年間）が高かったが（27.4% vs 14.7%， $p<0.001$ ），3年間の死亡率，入院率は男性要介護高齢者よりも女性で低かった（男性 vs 女性%，死亡率：31.3% vs 20.6%， $p<0.001$ ；入院率：48.6% vs 39.9%， $p<0.001$ ）。介護施設への入所は男性よりも高かった（5.2% vs 8.4%， $p=0.011$ ）。Cox 比例ハザード解析では男性と比較した女性要介護者の死亡，入院，施設入所のハザード・リスク（95% 信頼区間）は単変量解析でそれぞれ0.61（0.51～0.74），0.76（0.66～0.88），1.48（1.00～2.19）で，多変量解析ではそれぞれ0.51（0.39～0.66），0.83（0.69～0.99），1.19（0.73～1.93）であった。**結論：**在宅療養中の要介護高齢者は女性が多く，主介護者の続柄など介護環境に性差が存在する。さらに女性要介護高齢者では男性よりも3年間の死亡率は低いものの，介護施設へ入所する率が多いことが明らかとなった。

Key words：介護保険，要介護高齢者，在宅療養，介護保険サービス，性差

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緒 言

平成21年版 高齢社会白書によると，日本における高齢化はとどまることを知らず，平成20年度には65歳以上の高齢者人口は，過去最高の2,822万人となり，総人口に占める割合（高齢化率）も22.1%（前年21.5%）となり，22%を超える結果となった¹⁾。要介護高齢者の

数も急速に増加しており，特に75歳以上の後期高齢者で顕著である。介護保険制度における要介護者又は要支援者と認定された者のうち，65歳以上の者の数についてみると，平成18（2006）年度末で425.1万人となっており，高齢者人口の16.0%を占めている。75歳以上の人口について，要支援，要介護の認定を受けた者のそれぞれの区分における人口に対する割合をみると，75歳以上の人口で要支援の認定を受けた者は6.6%，要介護の認定を受けた者は21.4%となっており，75歳以上人口の25%以上が要介護・支援状態である。介護保険制度のサービスを受給した65歳以上の被保険者は，平成21年1月審査分で約368万人となっており，男女比で見ると男性が28.0%，女性が72.0%となっている（平成21年版 高齢社会白書より）¹⁾。

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これらより高齢者人口のかなりの数が要介護高齢者であり、さらにそのうち2/3以上を女性が占めていることがわかる。このように高齢者人口、要介護者集団においては数の上で明らかに性差があることが報告されている。しかし、その要介護高齢者の性別による背景(疾病構成、日常生活動作、精神心理的状态)、介護環境(独居状態、主介護者の有無、主介護者の背景、介護保険サービスの使用状況)の相違、さらには性別による予後、病院への入院、介護施設への入所に対するリスクの相違などは明らかではない。今回1,875名の在宅療養中に要介護者、ならびにその主介護者たちを対象にしたコホート調査を基に上記の疑問を明らかにする。

対象と方法

1. 対象者

名古屋市で行われた the Nagoya Longitudinal Study for Frail Elderly (NLS-FE) の登録時65歳以上であった高齢者のデータ(1,875名)を使用した。NLS-FEは名古屋市の17訪問看護ステーション併設居宅介護支援事業所を基盤とした訪問看護サービス利用者(65歳以上の高齢者)、訪問看護未利用者に、訪問看護師または介護支援専門員から書面で研究内容に関する説明をし、文書での同意を得られた要介護高齢者(1,875名)、さらにはその主介護者(1,568名)を調査対象(登録者)とする縦断的調査である。(登録は平成16年1月に終了)^{2)~5)}。登録者に関し、登録時に行った基本調査は1年ごとに行われ、経過中3年間、3カ月ごとにイベントの有無を調査した。イベントとは1)病院への入院(処置、検査入院を含む)、2)介護施設(老人保健施設、特別養護老人ホーム、グループ・ホームなど)への入所、3)死亡、4)脱落(訪問看護サービスの中止)を示す。なお、本研究は平成19年1月に終了している。

2. 基本調査内容

基本調査内容は a) 患者の属性 b) 社会的背景 c) 介護状態の把握 d) 看護サービス内容 e) 疾病背景 f) 既往歴(特に転倒、骨折) g) 身体機能ならびに精神心理機能(基本的ADL: Barthel index (range: 0~20)⁶⁾、認知症の有無、うつの有無: Geriatric depression scale short version (GDS-15, range: 0~15)⁷⁾ h) 栄養状態(身体計測、摂取状況を含む i) 併存症の評価: Charlson index (range: 0~9)⁸⁾ j) 薬剤調査 k) 主介護者の状態(健康状態、介護負担感(日本語版 the Zarit Burden Interview: ZBI))、看護師の主観的調査(サービス利用状況、患者の健康状況、家族の介護状況、主介護者の健康状況ならびに負担)などである。慢性疾患(冠

動脈疾患、心不全、脳血管障害、認知症、慢性閉塞性肺疾患、糖尿病、高血圧、悪性腫瘍)の有無はかかりつけ医からの情報を基に聴取された。さらに過去半年間の転倒歴、過去5年間の骨折歴を聴取した。これらの情報は本人または介護者、かかりつけ医からの情報を基にした。なお、GDS-15は認知症、またコミュニケーション不能者には実施しなかった。

3. 縦断調査

登録から3年間の経過中、イベント発生に関する報告書を看護師または介護支援専門員は記載し、3カ月ごとに名古屋大学に郵送した。イベントとは1)病院への入院(処置、検査入院を含む)、2)介護施設(老人保健施設、特別養護老人ホーム、グループ・ホームなど)への入所 3)死亡 4)脱落を示す。

4. 解析

登録時基本調査内容の男性・女性の相違、ならびに3年間の観察中に起こったイベント(死亡、入院、介護施設への入所)の性差を検討した。使用する解析法は student-t test, カイ二乗検定, Kaplan-Meier 検定, Cox 比例ハザード検定などを使用した。女性要介護者の男性要介護者と比較した死亡、入院、介護施設入所のリスクをCox比例ハザード検定で解析した。多変量解析では単変量解析で統計的有意($p < 0.05$)な因子をモデルに投入した。

5. 倫理面への配慮

本研究は名古屋大学倫理委員会の承認を得て実施した。十分なインフォームド・コンセントの後、必ず要介護者本人、主介護者の書面による同意書をもって登録とした。匿名化された情報は名古屋大学で厳重に管理し、全て集团的に分析し、個々のデータの提示などは行わず、個人のプライバシー保護に努めた。

結 果

表1に男女別登録された要介護高齢者ならびに主介護者背景を示す。登録された要介護高齢者は女性が明らかに多く(66.3%)、男性(33.7%)のほぼ2倍であった。年齢は女性81.5歳と男性78.8歳に比較し有意に高齢であった($p < 0.001$)。登録者のうち、独居で在宅療養中の要介護高齢者は女性で26.2%であり、男性14.6%に比較し有意に多かった。8割以上の要介護高齢者には主介護者が存在していたが、配偶者が主介護者である割合は女性の要介護高齢者で22.1%、男性で73.6%であった。主介護者介護負担感(ZBI)は男性要介護者の主介護者で有意に高かった。

登録時の平均基本的ADLならびにGDS-15得点は性

表 1 要介護者性別登録時の背景, 居宅サービス使用状況ならびにその主介護者の背景

	男性	女性	p
	n = 632, 33.7%	n = 1,243, 66.3%	
年齢, mean (SD)*	78.8 (7.6)	81.5 (7.5)	< 0.001
独居, n (%)	92 (14.6)	326 (26.2)	< 0.001
主介護者有無 (n = 1,568), n (%)			
有り	556 (88.0)	1,012 (81.4)	< 0.001
無し	76 (12.0)	231 (18.6)	
介護者女性, n (%)	482 (86.7)	697 (68.9)	< 0.001
介護者年齢, mean (SD)*	67.9 (11.2)	61.9 (12.7)	< 0.001
主介護者続柄, n (%)			
配偶者	409 (73.6)	224 (22.1)	< 0.001
嫁 (孫嫁を含む)	44 (7.9)	274 (27.1)	
子供	92 (16.5)	467 (46.1)	
兄弟 (姉妹)	4 (0.7)	30 (3.0)	
主介護者 ZBI, ** mean (SD)*	31.2 (17.2)	27.6 (16.8)	< 0.001
居宅サービス使用 (%)			
デイ・ケア (サービス)	43.5	43.9	0.865
訪問看護サービス	56.2	48.0	0.001
訪問介護サービス	43.2	48.8	0.021
定期的受診	61.7	58.4	0.164
ショートステイサービス	8.5	9.7	0.402
訪問入浴サービス	11.7	11.2	0.734
訪問リハビリテーションサービス	9.3	5.3	0.001
福祉用具レンタルサービス	65.8	56.3	< 0.001

* : student t-test, それ以外はカイ二乗検定

** : 日本語版 the Zarit Burden Interview (range : 0 ~ 88, n = 1,257)

差を認めなかった (表 2)。併存症の重症度のスケールとして使用した Charlson comorbidity index の平均得点は男性で高得点であり, より生命予後に係る併存症の集積が男性に認められた。定期的なかかりつけ医への受診率は性差を認めなかったが, 男性で多剤服用 (6 種類以上) が多かった (表 2)。慢性疾患の有病率では脳血管障害, 慢性閉塞性肺疾患, 悪性腫瘍は男性での有病率が有意に高かったが, 認知症は逆に女性で有意に高かった。過去半年間の転倒経験率は男女間で差を認めなかったが, 過去 5 年間の骨折の既往率は女性で有意に高かった (表 2)。

図 1 に男女別, 要介護度を示した。男女とも要介護 1 をピークとする分布を示し, ほぼ同様の分布であった。登録時の居宅サービスの使用率はデイケア (デイサービスを含む), ショートステイ, 訪問入浴サービスでは男女差を認めなかった (表 1)。一方, 訪問看護サービス, 訪問リハビリテーション, 福祉用具レンタルサービスの使用は男性でより高率で使用されていた。逆に訪問介護サービスは女性の要介護高齢者でより高率で使用されていた (表 1)。

3 年間の観察期間中に要介護者 1,875 名のうち, 454

人死亡し, そのうち 107 名が在宅での看取りであった。男性の死亡率は 3 年間で 31.3%, 女性は 20.6% で有意に男性の死亡率が高かった (表 3)。在宅死の率は男女の差を認めなかった。一方, 3 年間で一度でも入院を経験した要介護高齢者は 1,875 名のうち 803 名あり, 男女別では男性では 48.5% と女性 (39.9%) に比較し有意に高かった。介護施設への入所は逆に女性で高率 (男性 : 5.2% vs 女性 : 8.4%) であった (表 3)。

図 2 に男女別, 累積生存率, 累積入院率, 累積入所率を示す (Kaplan-Meier のプロット)。死亡, 入院に関しては有意に男性が女性に比較して高率であった。一方逆に女性の方が高い率で介護福祉施設に入所した。

性による 3 年間の観察期間における死亡, 入院, 介護施設入所に対するリスク差を明らかにするために, Cox 比例ハザード検定を行った。男性要介護者に比較し女性の死亡, 入院のハザード・リスク (HR) は単変量解析ではそれぞれ 0.61 (95% 信頼区間 (95%CI) : 0.51~0.74), 0.76 (0.66~0.88) で, 多変量解析ではそれぞれ 0.51 (0.39~0.66), 0.83 (0.69~0.99) であった (表 4)。一方, 介護施設入所の女性要介護者の HR (95%CI) は単変量解析では 1.48 (1.00~2.19) と有意差を認めたが, 多重

表2 男女別要介護者の背景ならびに併存症

	男性	女性	p
基本的 ADL (range: 0~20, mean (SD))*	12.6 (6.3)	12.8 (6.8)	0.496
GDS-15 (range: 0~15, mean (SD))*、†	6.8 (3.7)	6.4 (3.6)	0.064
Charlson index (mean (SD))*	2.4 (1.6)	1.8 (1.5)	< 0.001
定期的受診 (%)	61.7	58.4	0.164
服薬薬剤数 (%)			
0~2種類	16.5	24.7	
3~5種類	43.8	40.9	< 0.001
6種類以上	39.7	34.4	
慢性疾患の有無 (%)			
冠動脈疾患	12.3	12.1	0.888
慢性心不全	7.5	9.0	0.278
脳血管障害	46.6	28.3	< 0.001
慢性閉塞性肺疾患	9.9	5.9	0.003
糖尿病	13.2	11.4	0.280
認知症	31.7	37.0	0.031
高血圧	21.8	25.5	0.080
悪性腫瘍	12.9	7.3	< 0.001
転倒歴 (過去半年間) (%)	32.3	32.2	0.965
骨折歴 (過去5年間) (%)	14.7	27.4	< 0.001

* : student t-test, それ以外はカイ二乗検定

† : n = 1,409

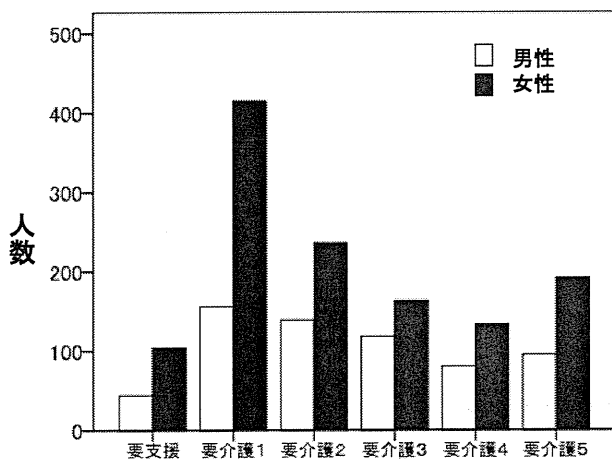


図1 男女別登録者の要介護度分布

解析では1.19 (0.73~1.93) と男性要介護者との有意な差は消失した (表4)。なお性差に要介護者年齢のみを調整因子として投入したモデルでも女性の入所リスクは1.30 (0.87~1.93), $p=0.195$ と有意差は消失していた。

考 察

高齢社会白書にあるように本コホートにおいても登録された要介護者は女性が男性のほぼ2倍を占めた。障害を持ちながらも居宅サービスを使用し、独居を継続している集団が存在したが、この集団は明らかに女性が多く、

男性に比較し要介護認定を受けていながらも自立した生活が女性では可能である場合が多い。このことは女性が元々身の回りのことを自分で長年こなしてきたという反面、男性は配偶者 (妻) に若い時より依存して生活をしてきたため、独居での生活が困難であるケースが多い、ということを表している可能性がある。厚生労働省「国民生活基礎調査」(平成19年)でも男性高齢者の独居率は10%前後である一方、女性高齢者では20~25%と高率である⁹⁾。

男性要介護者は主介護者が配偶者 (妻) であるケースは73.6%と高率であった半面、女性要介護者で主介護者が夫であるケースは22.1%と低かった。これは男性の方が短命であり、女性が要介護状態になった時点で、すでに夫が他界、または夫も要介護状態である場合が多いこと、さらには男性配偶者 (夫) は妻の介護をすることが困難である (しない)、ということを表しているのかもしれない。実際、総務省「国勢調査」では、男性高齢者は配偶者と生活しているものは平成17年の調査で81.8%、女性では47.1%と女性高齢者の約二人に一人は「配偶者なし」と報告されている⁹⁾。すなわち要介護状態になる以前より高齢者女性は配偶者と生活をしている数が男性高齢者より少ないことを意味している。これらの独居率さらには主介護者が配偶者である割合の性差は日本固有のものではなく、他の国でも同様との報告がなされているため¹⁰⁾、世界的に共通の事象なのかもしれない。

表3 男女別3年間に観察された各種イベントの発症率

各種イベント	男性		女性		p
	人数	%	人数	%	
全死亡	198	31.3	256	20.6	< 0.001
在宅死亡	36	5.7	71	5.7	0.989
入院	307	48.6	496	39.9	< 0.001
介護施設への入所	33	5.2	105	8.4	0.011

全てカイ二乗検定

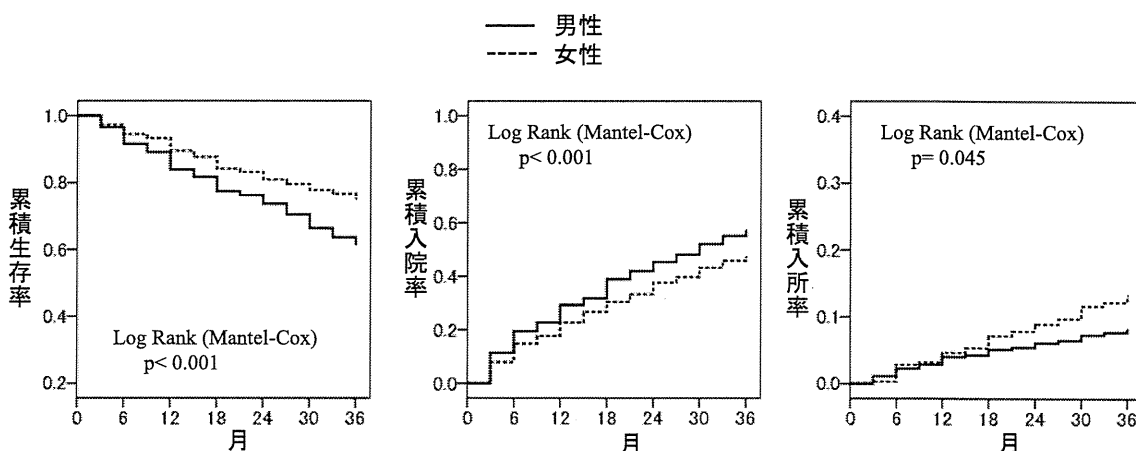


図2 男女別、累積生存率、累積入院率、累積入所率 (Kaplan-Meier のプロット)

表4 女性の種々のイベントに関するリスク (Cox 比例ハザード・モデル)

	univariate			multivariate		
	HR	95%CI	p	HR	95%CI	p
生命予後 女性 (vs 男性)	0.61	0.51 ~ 0.74	< 0.001	0.51	0.39 ~ 0.66 *	< 0.001
入院 女性 (vs 男性)	0.76	0.66 ~ 0.88	< 0.001	0.83	0.69 ~ 0.99 *	0.042
入所 女性 (vs 男性)	1.48	1.00 ~ 2.19	0.048	1.19	0.73 ~ 1.93 **	0.485

HR : Hazard ratio ; 95%CI : 95% confidence interval

* : 性, 年齢, 基本的 ADL score, GDS-15 score, Charlson index をモデルに投入

** : 性, 年齢, 基本的 ADL score, 介護者年齢, 主介護者 ZBI をモデルに投入

全米調査では女性の要介護者の独居率は男性に比較し有意に高く (女性 : 45.4%, 男性 16.8%), 本調査と同様に配偶者と生活している率は男性で高い (男性 : 73.6%, 女性 : 27.8%) ことが報告されている¹⁰⁾.

居宅介護サービスの使用に関しては、本調査時期と比較的近い平成 14 年の厚生労働省の報告によると、全国の居宅サービス利用者総数あたり、訪問介護利用率が最も多く 41.5%, 通所介護 (デイサービス) が 38.7%, 通所リハビリテーション (デイケア) が 20.8%, 訪問看護サービス 13.3%, 短期入所 (ショートステイ) 8.6% と

ある¹¹⁾. 本コホートでは訪問看護サービス使用が男性 56.2%, 女性 48.0% と明らかに利用率が高い. これは本研究対象者が訪問看護ステーションを基盤に登録をされたためである. 本調査では訪問介護サービス使用率が男性より、女性要介護高齢者に多かった. このことは一見矛盾するように思えるが、男性要介護者の主介護者の多くは配偶者 (妻) であるため、家事援助などの訪問介護サービスの使用が不必要である. 一方女性要介護者では配偶者 (夫) はすでに存在していないか、または主介護者として存在しているにも関わらず、十分な家事が実行