Basic and epidemiological research on the practical use of hormone replacement therapy for women's health and longevity

Year Three Report

Biological and Cultural Influences on Menopause (Kōnenki) in Japan

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The goals of this part of the project were to provide a descriptive natural history of the menopausal/midlife transition in Japan from: (1) an endocrinological/ physiological perspective (using hormone measures), (2) an ecological perspective (using food frequency questionnaires (FFQ), dietary records (DR) and measuring soy isoflavone concentrations), and (3) an experiential perspective (using symptom checklists, surveys, and interviews). Our main objective was to assess the influence of phytoestrogens on the endocrinology and symptomatology of the menopausal/midlife transition.

Briefly, in year 3, fieldwork in Fukushima was completed, with a total of 1538 matched blood samples and dietary records collected from a total of 77 midlife women (age 45-55 years). Method development for measurement of soy isoflavones (genistein, daidzein, and equol) in blood spot samples was begun, and preliminary analyses on the relationship between diet and health history were carried out for a subset of the data (Kyoto participants).

I. Fieldwork in Fukushima

Research began at the second field site, in Fukushima, Japan in October 2002 and ended in August 2002. The Fukushima research field team consisted of Melissa Melby (researcher), one research assistant for interviews, data and material preparation and organization, and one research assistant in Kyoto for data entry.

II. Screening and Enrollment

All women completed a screening interview (in person, by phone or by fax) to assess whether the potential participant met the exclusion/inclusion critieria and to assign menopausal status (based on menstrual period patterns). Women were excluded if they had taken hormones, had undergone hysterectomy, had both ovaries removed, had tubal ligation with subsequent menstrual changes, had taken hormones for menopause or birth control pill (in the last 5 years), had recent major illness, or were taking medication that could affect endogenous hormones.

The menopausal status on entrance to the study of participants by region is shown in **Table 1**. Premenopausal was defined as having reported a period in the previous 1 month with no changes in menstruation patterns in the past 12 months. Women reporting a period more than 3 months previous but less than 12 months prior to the screening interview, OR any changes in menstrual patterns in the past 12 months were classified as peri-menopausal. This group has been further divided into Perimenopausal I, defined as women who have experienced a period within the last 3 months, but some change in menstrual pattern in the last 12 months; and Perimenopausal II, defined as women whose last period was between 3 and 12 months prior to the screening date. Postmenopausal was defined as absence of menstrual periods for more than 12 months.

Table 1. Menopausal status at study entrance of women by region.

	Kyoto		Fukushima		Total	
	n	%	n	%	n	%
Pre	19	27.9	21	27.3	40	27.6
Peri	38	55.9	37	48.1	75	51.7
Peri I	27	39.7	29	37.7	56	38.6
Peri II	11	16.2	8	10.4	19	13.1
Post	11	16.2	19	24.7	30	20.7
Total	68	100.0	77	100.0	145	100.0

Compared to Kyoto, a higher percentage of the Fukushima participants were post-menopausal, and fewer were perimenopausal (II). Premenopausal women constitute similar proportions of each regional population.

III. Measures

A Single measures and questionnaires

- Screening Interview (prior to entry)
- Anthropometric measurements (weight, height, triceps skinfold, elbow breadth, and upper arm circumference)
- Initial Questionnaire (40 pages, 5 parts: Demographics, Health History, Reproductive History, Food Frequency Questionnaire, and Well-Being and Life Events)
- Headache Questionnaire (more detailed questionnaire on migraine headaches given to women who noted having headaches in past 2 weeks on initial questionnaire, or reported headaches on daily checklist)
- Daily Life semi-structured interview (tape-recorded) and usually done after 1 month of data had been received
- Final Questionnaire and Interview (Life history; checklist of konenki (menopause) symptoms, causes, and counter-measures; views on konenki, gender roles, and aging in general)

B. Measures taken for up to 6 months

- Daily symptom checklists
- Weekly 24-hour dietary records (on 24 hour period prior to blood spot sampling)
- Weekly blood spot samples (2 cards of 5 blood spots, taken 20 minutes apart)

IV. Data collected

Blood spot samples, weekly 24-hour dietary records, and daily symptom checklists were collected for 6 months by 60 women in Fukushima. Questionnaire data and 1 month of sample collection were obtained from 65 or more women (see Table 2).

Table 2. Types of data collected and number of women (n) from whom data have been received

Data	Fukushima (n)
Number of participants screened	114
Number of participants enrolled (signed consent forms)	77

Anthropometric measures	70
Initial questionnaire	73
Headache questionnaire	40
Daily life semi-structured interview	65
Final questionnaire and interview	62
1 month of BS samples, weekly 24 hour dietary records, and daily symptom checklists	65
3 months of BS samples, weekly 24 hour dietary records, and daily symptom checklists	64
6 months completed	60
Daily symptom checklists (in weeks)	1528
Dietary records (DR) (1 per week)	1553
Blood spot samples (1 per week)	1584
Matched BS and DR (weeks)	1538

V. Development of method for measurement of soy isoflavones.
Originally we proposed to use time resolved fluorescence immunoassay (TR-FIA) to measure the soy isoflavones genistein and daidzein. However, we have instead chosen to develop a method using high performance liquid chromatography (HPLC) with multichannel coulometric electrochemical detection (ECD) because the latter will enable us to measure 3 isoflavones (genistein, daidzein and equol) in the same sample. The health benefits of soy appear to differ in people who are able to metabolize daidzein to equol (equol producers) and those who cannot (equol non-producers), and thus it is imperative that we be able to measure equol in our samples. We are currently modifying published literature protocols [1, 2] for use with dried finger-prick blood spots and plan to analyze the collected blood spots by this method during the next year.

VI. Preliminary report on 'Seasonal phytochemical intake by Kyoto women and relationship to health history' (an abridged version of this report is currently in press)

INTRODUCTION

Recently researchers have been looking beyond macro- and micronutrients to the role of functional food factors (FFFs) in health and disease [3-5]. Reports of the health benefits of soy isoflavones such as reducing menopausal symptoms and lowering cholesterol are increasing in the popular press, and other foods and drinks such as green tea have been touted for their health benefits. We examined the effects of phytochemicals on the health of Japanese women in midlife and identified factors that may influence health status in later years.

SUBJECTS AND METHODS

One-day dietary records including the name of dish, constituent foods and their amounts were self-described weekly by each participant for 6 months. Dietary records were coded and data entered by 5 nutritionists using the Standard Tables of Food Composition in Japan [6]. These tables contain 1882 foods in 18 food groups, with average macro- and micronutrient values, which were used to estimate individual daily average intake. Daily average phytochemical or functional food factors (FFF) were estimated using a recently developed FFF database containing 57 phytochemicals in 278 foods, which can be found at http://www.life-science.jp/FFF/seibunfff.jsp.

Individual seasonal average nutrient and FFF values (µmol/day/person) were calculated and analyzed for seasonal differences using the Kruskal-Wallis non-parametric test (FFF values were not normally distributed). Monthly FFF intake averages were calculated and used for graphs of phytochemicals with significant seasonality. Principal component analysis was performed on a subset of 47 phytochemicals using Varimax rotation with Kaiser Normalization to identify phytochemical factors in the daily diet records. Phytochemicals with a 90th percentile of zero over the entire study period were eliminated from the factor analysis. Individual average phytochemical factor values were calculated for the entire study period, and used in logistic regression to identify the relationships between phytochemical factors and health conditions. Models were built using backward stepwise selection (probability for stepwise removal = 0.10). Odds ratios (OR) are reported as Exp(B) along with 95% C.I. and p-values for all variables included in the final model. Dependent binary variables examined were: hot flash and vasomotor symptoms (including sweats) during previous 2 weeks; and history of hypertension, diabetes, allergy, menopausal syndrome, and migraine. Covariates included in each model were 17 phytochemical factors, BMI, age (yrs), and menopausal category (MPcat). Women were assigned to pre-, peri-, or post-menopausal groups according to their menstrual patterns on entrance to the study (pre: no change in previous 12 months; peri: change in timing, duration and/or flow during past 12 months; post: no menstrual bleeding in past 12 months). SPSS (version 11.5) was used for all statistical analyses. A p-value of less than 0.05 was considered significant ($p < 0.1$ was considered a trend).

RESULTS

Subject characteristics

Data from 67 women were analyzed, providing a total of 1528 dietary records spanning 11 months from December 2001 – October 2002. Participants included 18 premenopausal (26.9%), 38 perimenopausal (56.7%), and 11 postmenopausal (16.4%) women with age ranging from 45-55 yrs (49.3 ± 2.8 yrs). The population averages (mean ± SD) were: height 156.5 ± 4.8cm, weight 57.0 ± 8.9kg, and BMI 23.3 ± 3.7. Fifty-eight women (86.6%) completed 24 weeks of 24-hour dietary records, 62 women (92.5%) completed 9 weeks or more, and 5 women (7.5%) completed 5 weeks or less. The average energy and nutrient intakes for all 1528 dietary records are summarized in **Table 3**.

Phytochemical seasonality

In addition to calculating macro- and micronutrient intake, we calculated the intake of 56 phytochemicals (including 6 carotenoids, 7 sulfur-containing compounds, 21 flavonoids, 3 isoflavones, 4 catechins, 7 anthocyanins, 8 organic acids) and total polyphenols. No significant seasonality was observed in any nutrient (Kruskal-Wallis non parametric test P = 0.03) with the exception of folic acid, which ranged from an autumn low of 254.72 ± 59.65 to a winter high of 316.86 ± 107.69 (mean ± SD, µmol/day/person).

Significant seasonality was observed in 26 of 57 (45.6%) phytochemicals calculated. **Table 4** shows seasonal means, SD, medians, 90th percentile, and results of the Kruskal-Wallis nonparametric test. **Figure 1** shows monthly means (arranged by chemical class) for the 26 phytochemicals that displayed significant seasonal variation. Phytochemicals displaying a winter maximum include: isothiocyanate, S-allyl-L-cysteine sulfoxide, S-propyl-L-cysteine sulfoxide, hesperitin, diosmin, nobiletin, neoponcirin, rutin, (+)-catechin, and caffeic acid. Phytochemicals exhibiting a spring maximum include: cryptoxanthin, S-methyl-L-cysteine sulfoxide, chrysoeryol, eriocitrin, rhoifolin, neohesperidin, pelargonin, cyanidin, and pelargonidin. Phytochemicals reaching their peak intake levels during summer are the following: lycopene, naringenin, luteolin, anthocyanidin, benzoic acid analogs, and ferulic acid. Only S-1-propenyl-L-cysteine sulfoxide displayed an autumn maximum (with secondary maximum in spring) in this study.

Phytochemical factor analysis and relationships to health history

Seventeen phytochemical factors (F1 - F17) were extracted from 47 phytochemicals in 16 iterations, and these factors explained 77% of the variance. Factors and their component phytochemicals are shown in **Table 5**, along with the chemical class and primary foods for each phytochemical.

Logistic regression models for hypertension, diabetes, allergy, migraine, menopausal syndrome, and vasomotor symptoms identified relationships between 16 of the 17 phytochemical factors, age, BMI and MPcat (**Table 6**). To the extent that current diet reflects past diet in this population, a negative correlation or an Exp(B) < 1 (or OR < 1) indicates a possible preventive factor, and a positive correlation between a factor and health outcome, or Exp(B) > 1 (or OR > 1), is suggestive of an exacerbating or risk factor.

In the model for hypertension, age and phytochemical F8 and F13 showed OR < 1, while F6, MPcat, and BMI showed an OR > 1. In the final model for diabetes, F8 and F11 showed an OR < 1, and F12 showed an OR > 1. Many potentially protective phytochemical factors were identified for allergy (F1, F8, F10, F17) and migraine (F6, F7, F8, F14, and F17), while few factors were positively correlated (F12 for allergy, and F1 and F16 for migraine). Factors included in the model for menopausal syndrome which had Exp(B) < 1 were F1, F2, and F11, while F3, F5, F9, and F16 showed Exp(B) > 1 for menopausal syndrome, hot flash, and/or vasomotor symptoms. Factor 4 and F15 were not included in any of the final models.

DISCUSSION

Phytochemical seasonality

In contrast to a previous study in Japan [7], no significant seasonality was observed in nutrient intake (with the exception of folic acid), but significant seasonality was found for 26 phytochemicals, suggesting that measures of diet at one or few time points may be misleading if consumption of biologically active food factors is seasonal – even in industrialized countries such as Japan. Researchers in nutritional epidemiology are often concerned that within-person variation in dietary intake (or random fluctuation around a person's true long-term average) may distort correlation coefficients, regression coefficients, and relative risks, thereby reducing the strength of associations [8], but much of this variation may be seasonal and thus non-random.

Sulfur compounds derive from foods such as onion, broccoli, cabbage and daikon that are generally eaten in the winter in Japan. Many flavonoids such as hesperetin showed a large increase in winter, and cryptoxanthin showed a large increase in winter and spring, probably due to consumption of Satsuma mandarin oranges and other citrus fruits such as grapefruit. Lycopene, which derives mostly from tomatoes, showed a significant increase in summer. Intake of ferulic acid and anthocyanidin were higher in summer and autumn, probably due to consumption of late summer vegetables such as eggplant.

Despite literature reports of autumn peaks for dietary and/or plasma phytochemicals such as beta-carotene [9, 10], we found an autumn maximum only for S-1-propenyl-L-cysteine sulfoxide (nor did we find seasonal patterns for beta-carotene). As autumn dietary records were only collected from 21% of our population, sample size limitations may have prevented the detection of significant autumnal peaks. When data were reanalyzed without dietary data from autumn to assess whether there were differences in seasonal means of winter, spring and summer, no differences were found (i.e., the same phytochemicals were identified as having significant seasonality) (data not shown).

Relationships between phytochemical intake and health

Participants with greater intake of sulfur compounds (F8 and F14) were less likely to suffer from hypertension, diabetes, allergy and migraine. These compounds are found primarily in foods such as onions, broccoli, daikon and cabbage, and showed winter maxima (often more than double the summer intake). These results suggest that studies carried out during the summer may underestimate intake of sulfur compounds that may have significant protective effects on many health conditions. Participants consuming greater amounts of flavonoids (F2, F7, F11, F13) were less likely to have experienced menopausal syndrome, migraine, diabetes, hot flash and hypertension (respectively). Flavonoids, many of which exhibit peak intakes in winter and spring, should be investigated further in terms of their protective benefits. Factors containing organic acids (deriving from eggplant, komatsuna, sweet corn) and carotenes (from seaweed, mandarin orange and red pepper) (F10, F17) also showed negative relationships with allergy and migraine.

Protective effects of fruits and vegetable intake are well known, but several phytochemical factors exhibited increased OR for menopausal symptoms and other health conditions. Catechins (F3), which are found in tea, may exacerbate hot flashes and vasomotor symptoms and also exhibited a higher OR for diabetes (F12). In Kyoto, where many middle-aged women practice the traditional Japanese art of 'tea ceremony', or drink tea in social groups, tea intake usually occurs simultaneously with consumption of sweets with very high sugar content. Thus the apparent connection between diabetes and tea intake, may actually be an indirect correlation, with the salient food being the sweets consumed at the same time as the tea. However, BMI was not included in the final logistic regression model for BMI. Myricetin (found in bananas and black tea) and total polyphenols (F16) showed an increased OR for menopausal syndrome and history of migraine. Intake of caffeine, which is found in tea and thus correlated with catechin intake, has been observed to trigger, as well as alleviate and prevent headaches [11-13]. Participants with a history of menopausal syndrome also reported higher intake of anthocyanins, found in fruits such as strawberries and limes.

Phytochemicals have evolved to fulfill many functions of plants ranging from maintenance, reproduction, and defense against herbivores and disease. Given their range of activity and ecological context, both positive and negative effects on human physiology should be expected [14]. In this study, several phytochemical factors showed both positive and negative relationships with different health conditions, suggesting that FFFs exhibit complex interactions with the human body, and that an individual's health history should be considered when recommending intake of various phytochemicals (particularly in supplement form). Factor 1, containing mostly carotenes deriving from carrot, pumpkin, and moroheiya (*Corchorus olitorius*), exhibited a protective relationship against allergy, menopausal syndrome, and hot flashes, but consumption of such FFFs may increase migraine. Consumption of the 2 sulfur compounds and 1 flavonoid commonly found in onions (F6), appears to be protective against migraine but contra-indicated for hypertension. Participants with higher intake of 2 organic acids and an anthocyanin commonly found in eggplant, grapes, burdock, peach, and moroheiya (F9) were more likely to report previous history of menopausal syndrome, but less likely to have experienced vasomotor symptoms in the previous 2 weeks. Different results for menopausal syndrome and vasomotor symptoms support the observation that vasomotor symptoms may not be a hallmark of Japanese menopausal syndrome as they are in the West [15].

Soy isoflavones (F4) were not included in any of the final logistic regression models. The effects of soy on menopausal symptoms have been widely studied [16-18] and are often used to promote soy products in the West. Our study, however, did not find any correlation (good or bad) between soy and menopausal symptoms, but found instead that flavonoids from citrus and carotenes from carrot and pumpkin were correlated with lower incidence of menopausal syndrome, and anthocyanins were correlated with higher incidence. While positive correlations between age and BMI and vasomotor symptoms were expected [19], positive relationships between consumption of phytochemicals found in tea were not. Tea (particularly green tea consumed widely in Japan) is often touted for its health effects, but these results suggest that it may be contraindicated for some health conditions such as vasomotor symptoms at menopause and possibly diabetes.

In summary, significant seasonality was observed for 26 phytochemicals. Measures of dietary intake at one time point or in one season may lead to inaccurate estimations of the intake of important FFF, many of which display significant seasonality and appear to have both positive and negative relationships with various health outcomes.

VII. REFERENCES

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Table 3. Macro- and micronutrient intake

(n = 1528 24-hour dietary records from 67 women)

	Mean ± SD	Median
Intake (g)	1674.04 ± 528.16	1615.44
Energy (kcal)	1712.47 ± 416.50	1716.50
Energy (kJ)	7161.59 ± 1742.06	7180.00
Water (g)	1303.09 ± 472.89	1239.70
Protein (g)	67.26 ± 20.81	65.30
Lipid (g)	54.27 ± 21.89	51.40
Carbohydrate (g)	230.11 ± 61.04	227.10
Ash (g)	15.62 ± 5.22	14.90
Sodium (mg)	3212.68 ± 1345.39	3025.50
Potassium (mg)	2426.32 ± 894.11	2301.50
Calcium (mg)	519.30 ± 253.93	480.00
Magnesium (mg)	255.78 ± 94.06	241.50
Phosphorus (mg)	1014.74 ± 333.52	977.00
Iron (mg)	7.41 ± 3.01	6.90
Zinc (mg)	7.58 ± 2.73	7.20
Copper (mg)	1.07 ± 0.41	1.01
Retinol (μg)	245.64 ± 644.64	152.00
Carotene (μg)	3195.23 ± 2999.84	2424.00
Vitamin A (μg) [1]	785.38 ± 874.36	602.00
Vitamin D (μg)	7.30 ± 8.72	4.00
Vitamin E (mg)	8.11 ± 3.59	7.55
Vitamin K (μg)	218.08 ± 186.43	155.00
Vitamin B1 (mg)	0.87 ± 0.40	0.79
Vitamin B2 (mg)	1.10 ± 0.43	1.06
Niacin (mg)	16.44 ± 7.18	15.50
Vitamin B6 (mg)	1.14 ± 0.48	1.08
Vitamin B12 (μg)	6.51 ± 6.67	4.20
Folic Acid (μg)	303.08 ± 159.80	273.00
Pantothenic Acid (mg)	5.38 ± 1.91	5.17
Vitamin C (mg)	95.57 ± 65.26	80.00
Saturated Fat (g)	15.61 ± 7.69	14.47
Monounsaturated Fat (g)	18.37 ± 8.53	17.14
Polyunsaturated Fat (g)	11.82 ± 5.68	10.81
Cholesterol (mg)	316.94 ± 186.65	291.50
Water Soluble Fiber (g)	3.05 ± 1.43	2.80
Insoluble Fiber (g)	9.89 ± 4.29	9.05
Total Fiber (g)	13.70 ± 5.83	12.60
Sodium Chloride (g)	8.14 ± 3.43	7.60
Manganese (mg)	2.67 ± 1.14	2.49
Nitrogen (g)	9.31 ± 3.11	8.98

1 = Retinol equivalents

Table 4. Phytochemical intake (µmol/day/person) by season for phytochemicals with significant seasonality (n = number of participants)

Phytochemical	Sig[1]	P[2]	Winter (n = 50) Mean[3]	SD	Med	90%ile	Spring (n = 65) Mean[3]	SD	Med	90%ile	Summer (n = 48) Mean[3]	SD	Med	90%ile	Autumn (n = 14) Mean[3]	SD	Med	90%ile
CAROTENES																		
cryptoxanthin	**	0.005	3.98	26.38	0.14	0.80	**4.22**	32.37	0.14	0.55	0.10	0.09	0.08	0.21	0.07	0.11	0.03	0.29
lycopene	***	0.001	0.68	1.80	0.00	1.92	0.86	1.59	0.02	2.71	**2.27**	3.06	1.35	6.70	0.73	1.63	0.01	4.03
SULFUR COMPOUNDS																		
isothiocyanate	*	0.015	**27.11**	17.29	22.50	49.75	22.54	15.50	18.00	42.96	19.52	17.95	14.02	55.86	20.21	20.66	11.09	62.04
S-1-propenyl-L-cysteine sulfoxide	†	0.079	681.68	551.38	539.07	1450.45	862.88	502.02	759.18	1521.90	691.14	456.58	613.86	1243.48	**890.27**	1036.55	669.59	2890.49
S-allyl-L-cysteine sulfoxide	***	0.001	**68.63**	72.52	45.24	160.10	43.28	41.62	28.31	96.15	22.03	23.50	14.15	63.94	28.53	18.51	28.99	54.48
S-methyl-L-cysteine sulfoxide	†	0.093	106.67	80.21	84.68	234.28	**112.28**	64.10	104.05	186.38	83.33	52.80	76.60	156.23	107.91	106.31	84.96	309.78
S-propyl-L-cysteine sulfoxide	**	0.001	**401.54**	410.09	256.87	899.57	268.73	233.78	201.35	502.23	147.56	133.97	107.43	381.35	182.89	96.51	181.07	328.02
FLAVONOIDS																		
hesperetin	**	0.006	**84.09**	106.11	36.69	242.44	41.24	112.27	5.60	111.70	54.04	122.74	0.00	278.76	42.80	57.90	11.31	145.00
naringenin	*	0.029	20.41	72.25	0.00	35.81	32.18	72.43	1.05	110.53	**49.38**	105.30	0.00	172.54	8.72	19.69	0.00	47.78
luteolin	*	0.013	0.77	2.59	0.00	1.22	0.91	1.10	0.63	2.24	**1.19**	1.56	0.68	4.09	0.96	1.59	0.24	3.98
neohesperidin	†	0.079	0.94	3.65	0.00	1.86	**1.65**	3.43	0.00	4.99	1.46	4.28	0.00	4.85	0.51	1.15	0.00	2.78
neoponcirin	**	0.003	**1.77**	2.38	0.79	5.62	0.50	0.88	0.04	1.69	0.37	0.72	0.00	1.21	0.77	0.99	0.38	2.64
rutin	**	0.001	**0.54**	0.77	0.23	1.85	0.13	0.26	0.00	0.53	0.09	0.16	0.00	0.29	0.24	0.35	0.00	0.89
chrysoeryol	†	0.081	0.08	0.22	0.00	0.39	**0.12**	0.42	0.00	0.34	0.06	0.24	0.00	0.12	0.00	0.00	0.00	0.00
diosmin	***	0.000	**0.44**	0.69	0.15	1.57	0.05	0.21	0.00	0.11	0.04	0.10	0.00	0.21	0.24	0.35	0.00	0.89
eriocitrin	*	0.024	0.06	0.33	0.00	0.00	**0.13**	0.41	0.00	0.26	0.04	0.17	0.00	0.01	0.00	0.00	0.00	0.00
nobiletin	**	0.001	**0.11**	0.36	0.00	0.37	0.02	0.08	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
rhoifolin	**	0.010	0.05	0.18	0.00	0.12	**0.23**	0.52	0.00	0.64	0.19	0.50	0.00	0.79	0.00	0.00	0.00	0.00
CATECHINS																		
catechin	***	0.000	**4.87**	6.91	2.70	13.82	4.71	8.52	2.15	11.98	1.95	4.27	0.00	6.05	1.88	3.68	0.12	9.19
ANTHOCYANINS																		
anthocyanidin	***	0.000	3.60	6.31	0.00	11.83	9.46	8.80	7.73	23.39	**18.93**	18.82	16.33	49.65	13.02	12.49	12.45	34.73
cyanidin	†	0.077	0.44	0.76	0.00	1.77	**0.73**	1.02	0.24	2.28	0.71	2.37	0.00	1.57	0.61	0.98	0.11	2.67
pelargonidin	***	0.000	1.14	1.97	0.00	4.59	**1.83**	2.57	0.63	5.84	0.08	0.57	0.00	0.00	0.05	0.12	0.00	0.32
pelargonin	***	0.000	0.21	0.36	0.00	0.83	**0.33**	0.47	0.11	1.05	0.02	0.11	0.00	0.00	0.01	0.02	0.00	0.06
ORGANIC ACIDS																		
benzoic acid analog	***	0.000	0.18	0.89	0.00	0.00	0.05	0.30	0.00	0.00	**3.13**	7.16	0.00	14.23	0.00	0.00	0.00	0.00
caffeic acid	***	0.000	**6.94**	42.67	0.58	2.66	5.53	27.49	1.84	4.82	3.31	3.04	2.06	7.19	2.29	1.80	1.62	5.29
ferulic acid	***	0.000	4.76	8.00	1.64	13.23	7.91	8.06	6.10	20.45	**20.22**	20.19	14.98	52.13	13.51	12.95	13.09	37.30

1 Significance: *** p < 0.001; ** p < 0.01, * p < 0.05; † p < 0.1 2 p-value from Kruskal-Wallis nonparametric test (df = 3, N = 177) 3 Bold values denote seasonal maximum mean intake

Table 5. Phytochemical Factors (extracted from 1528 dietary records) and their chemical subclasses and primary foods[1]

Factor	Subclass	Component Phytochemicals	Primary foods
F1	carotene	beta-carotene	carrot, pumpkin, moroheiya (*Corchorus olitorius* L.)
	carotene	lutein	pumpkin, moroheiya, cucumber
	flavonoid	kaempferol	kale, komatsuna, moroheiya
	carotene	alpha-carotene	carrot, purple laver (seaweed)
F2	flavonoid	poncirin	grapefruit
	flavonoid	neohesperidin	grapefruit, sudachi fruit
	flavonoid	naringenin	grapefruit, tomato
	flavonoid	apigenin	parsley, grapefruit, Malabar nightshade
	carotene	lycopene	tomato, watermelon
F3	catechin	catechin analog	
	catechin	epigallocatechin	tea (sen-cha, oolong tea, ban-cha)
	catechin	epicatechin	tea (sen-cha, ban-cha, oolong tea)
F4	flavonoid	daidzein	soybeans and soy products (natto, tofu, miso)
	flavonoid	glycitein	soybeans and soy products (natto, tofu, miso)
	flavonoid	genistein	soybeans and soy products (natto, tofu, miso)
F5	anthocyanin	pelargonin	strawberry
	anthocyanin	pelargonidin	strawberry, cherries
	anthocyanin	cyanidin	lime, pomegranate
F6	sulfur compound	S-1-propenyl-L-cysteine sulfoxide	onion
	flavonoid	quercetin	onion, tomato, moroheiya
	sulfur compound	S-methyl-L-cysteine sulfoxide	onion
F7	flavonoid	diosmin	lemon, Satsuma mandarin orange
	flavonoid	neoponcirin	Satsuma mandarin orange, navel orange, grapefruit
	flavonoid	rutin	buckwheat, Satsuma mandarin orange
	flavonoid	eriocitrin	lemon, navel orange, sudachi fruit
F8	sulfur compound	S-allyl-L-cysteine sulfoxide	onion
	sulfur compound	S-propyl-L-cysteine sulfoxide	onion
F9	organic acid	ferulic acid	eggplant, bread, white rice
	anthocyanin	anthocyanidin	eggplant, grapes
	organic acid	cinnamic acid	burdock, peach, moroheiya
F10	organic acid	caffeic acid	coffee, eggplant, komatsuna
	carotene	cryptoxanthin	purple laver (seaweed), papaya, Satsuma mandarin orange
	organic acid	chlorogenic acid	coffee, eggplant, peach
F11	flavonoid	narirutin	grapefruit, Valencia orange, Satsuma mandarin orange
	flavonoid	hesperetin	Valencia orange, Satsuma mandarin orange, navel orange
F12	catechin	catechin	peach, apple

F13	flavonoid	chrysoeryol	celery
	flavonoid	luteolin	green and red peppers, sweet peppers
F14	sulfur compound	4-methylsulfinylbutyl isothiocyanate	broccoli
	sulfur compound	isothiocyanate	daikon (Japanese radish), cabbage, wasabi
F15	flavonoid	rhoifolin	Satsuma mandarin orange, pummelo, sour oranges
	organic acid	protocatechuic acid	grapes
	organic acid	gallic acid	grapes, pineapple
F16	flavonoid	myricetin	banana, black tea
		total polyphenols	fruits and vegetables
F17	carotene	zeaxanthin	purple laver (seaweed), red pepper
	organic acid	benzoic acid analog	sweet corn

1 Factor analysis was performed only with phytochemicals with total 90 percentile>0 using 1528 1-day dietary records.
Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization.
Rotation converged in 16 iterations. 17 factors explained 77% of the variance.

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分担研究報告書
女性の健康と健康リスクについての関連性の分析

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研究要旨　第3年度は乳がんや子宮がんの市区町村を単位とした経験ベイズ推定に基づくEBSMRを指標として、検診受診率（平成7年から11年までの総和）との関連性を回帰分析により検討した。その結果乳がん、子宮がんともに検診受診率が高いと死亡率が低いという関連性が認められた。この結果は検診受診率の影響は経年的に変わらないという仮定の下で検討したものであり、今後、県単位などの地域差や他の交絡要因や環境等の違いも含めてさらに詳細に検討する必要があろう。一方、女性の自覚的健康満足度に及ぼす社会文化的要因の影響の分析を、最近行われた東アジア国際比較の調査結果から、自覚症状の比較分析を行った。その結果、他の東アジア諸国と比べても欧米諸国との比較結果と同様に自覚的症状の訴えは少なかったが、日本人では男性に比べ女性の方がいずれの年齢層においても訴えは高かった。これらの訴えは生活満足度の高さや信頼感、不安感とも関連し、そのほか、不眠の訴えでは高年齢等も関連していた。

1．EBSMRに基づく市区町村別乳がんおよび子宮がん死亡の評価

A. 研究目的

平成14年度の研究では、人口サイズの影響を調整した経験的ベイズ推定としてのEBSMRを算出し、これにより女性特有の疾患として乳がんと子宮がんの死亡に焦点をあて、死亡状態の評価を行った。これまで広く利用されてきたSMRは、市区町村別死亡率の評価を行うにあたり、特に人口サイズの小さな地域での人口サイズのバラツキの影響を受け、結果の誤った解釈につながる可能性を否定できず、EBSMRは地域評価においても有効な指標である（丹後, 1999, 2000）。本研究では、乳がんおよび子宮がん検診とそれぞれの疾患の死亡率との関連を検討した。

B.　研究方法

死亡率のデータは、乳がんおよび子宮がん死亡に関するSMRを「健康・体力づくり事業財団」平成7-平成11に関する報告を利用し、この5年間でSMRの得られている年度について死亡数と期待死亡数を求め、日本全国を基準としたときの期待死亡数を算定し、これを基に市区町村別EBSMRを算出したものである。なお、後者の場合には期待死亡数が0のときは推定できないため、0.5を代入して推定した。がん検診受診率のデータは、「健康・体力づくり事業財団」平成7-平成11報告を利用し、5年間での総対象数、総受診数から受診率を求めたが、この際にも2項分布を仮定した経験ベイズ推定による受診率を求めた。がん検診受診率と死亡率との関連は回帰分析により検討した。この解析は、検診受診率の地域格差は経時的に変化せず5年間の受診率で

代表され、その死亡に対する影響も同等であるという強い仮定の下で行っており、解析結果の解釈の際にはその点に留意する必要がある。なお、解析にあたってはがん検診受診率と死亡率ともにその分布を考慮し対数変換をしたデータを用いた。

C. 研究結果

EBSMR を指標とした乳がん（図１）、子宮がん（図２）では、ともに検診受診率が高いことと死亡率が低いという統計的に有意な関連性が認められた(いずれも p<0.0001)。なお、通常の SMR で見た場合にはいずれも関連性の p 値から見た有意性は弱くなっていた（乳がん、子宮がんではそれぞれ 0.0014、0.0295)。

D. 考察

SMR を利用して乳がんや子宮がんなどの市区町村別死亡率の評価を行う場合には、特に人口サイズの小さな地域でのバラツキの影響を受け、結果の誤った解釈につながる可能性を否定できない。そのためには、人口サイズの影響を調整した経験的ベイズ推定としての EBSMR による評価が有用である。そこで本研究では EBSMR を利用して死亡状態の評価を行い、検診受診率との関連を分析した。

回帰分析の結果は、検診受診率の影響は経年的に変わらないという強い仮定の下で検討したものである。乳がんに関しては、久道らの報告でも検診の効果があることが報告されており、今後さらに県による地域差や他の交絡要因、環境等の違いも含めて詳細に検討する必要があろう。この際には、県別に解析を行う、あるいは階層構造を仮定した変数効果モデルなどを利用して分析することも考えられよう。また、地域集積性の比較検討をすることなども今後の課題である。

E. 結論

本研究では、乳がんや子宮がんなどの女性特有の疾患に焦点をあて市区町村を単位とした EBSMR を元に、検診受診率との関連性について検討した。日本全国を総じて関連性の検討を行ったところ、乳がん、子宮がんでは統計的に検診の効果が認められた。今後さらに詳細な検討が必要とされる。

F. 知的所有権の取得状況

特記すべきことなし

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2．東アジアにおける自覚症状に及ぼす要因の国際比較

A. 研究目的

疫学班では昨年度の研究の一環として、既存の確率標本により得られた７カ国国際比較調査からの実証的データを基に、女性の自覚症状に着目し、女性の自覚症状に及ぼす教育、経済、学歴、家庭満足度、信頼感など社会文化的要因の影響の分析を行い、日本の女性の特徴の一端を明らかにした。しかし、これらのデータは 1990 年前後のものであり、最新のデータによる検討が必要とされた。

本年度は、女性の自覚的健康満足度とそれに及ぼす社会文化的要因の影響の分析を、最近行われた大規模確率標本に基づく東アジア国際比較調査結果の調査結果を用いて行った。

B. 研究方法

東アジア国際比較調査は、各国において大規模確率標本に基づく面接調査として行われたものであり、詳細は（吉野 2002, 山岡 2003）に記載されている。

自覚症状は、前年度の7カ国国際比較調査の分析と同様に、頭痛、背中の痛み、いらいら、うつ状態、不眠症の5項目（フランスのCREDOC で用いられた5項目）についての1個以上症状有りを取り上げた。さらに不眠症の訴えの有無を取り上げた。データはすべて頻度にまとめ、国別、性、年齢階級別データとして比較した。

関連する項目としてここでは年齢(5階級)、社会階層意識（5段階）、生活満足度（4段階を「やや満足以上」と「その他」の2区分とした)、不安感（3項目に関する不安と回答した個数)、信頼感を取り上げた。信頼感は米国General Social Survey(GSS)で用いられている”trust”の3項目を取り上げ､それの反応個数を用いた。以上を要因として、国別にロジスティック回帰分析を行い、関連する項目について検討した。

C. 研究結果

(1) 年齢別自覚症状の訴えの比較

昨年度報告した7カ国国際比較調査結果（1990年前後）では欧米諸国に比べて日本人は訴えが少ない方であったが、最近の日本人の調査結果(2002 年)でも他の東アジア諸国と比べて自覚的症状の訴えは男女とも少なく、特に5症状(女性)とその中の不眠の訴え(男女とも）に関してはほとんどの年齢層において少なかった（図3)。また、女性では身体関連の3項目のみとした場合でも最も少なかった（図4)。不眠の訴えでは日本人は男女とも最も少なかった（図5)。なお、日本人では男性に比べ女性の方がいずれの年齢層においても訴えは高かった。

(2) 自覚症状に及ぼす要因の分析

年齢、社会階層意識（5段階)、生活満足度（2段階)、不安感、信頼感を取り上げ、ロジスティック回帰分析により、症状の訴えの多さに関連する項目について検討した。その結果、日本人でのこれらの訴えは男女とも生活満足度の高い方で低い傾向が認められ、さらに男性では不安感が高いと訴えも高い、女性では信頼感が高いと訴えは低く、年齢が高い方で訴えも高いという傾向が認められた。一方、不眠の訴え関しても同様に分析したところ、男女とも信頼感が高いと不眠の訴えは低く､高年齢になるほど高い傾向が認められた。さらに男性では生活満足度が、女性では不安感が関連していた。

D. 考察

東アジア諸国として日本、韓国、台湾、中国（北京、上海、香港）の大規模確率標本による調査結果に基づき、女性の自覚症状5項目あるいはその中の身体症状に関する3項目でのいずれかの症状の訴え、および不眠の訴えに着目し、国別に属性および社会文化要因との関連性の比較を行った。その結果、東アジアにおいても欧米諸国との比較結果と同様に症状を訴える傾向は日本では少ない傾向を示していた。要因分析の結果では若干の相違はあったものの、症状の訴えには生活満足度や信頼感、不安感の関連が強く、不眠ではさらに高年齢などとの関連が示唆された。

E. 結論

既存の意識の国際比較に関する東アジア諸国の最近のデータを基に､女性の自覚症状に及ぼす社会文化的要因の影響の分析を行ったところ､日本は東アジア諸国の中でも訴

えは低い方であったが、女性は男性に比べてやはり高い傾向を示した。

F. 知的所有権の取得状況

特記すべきことなし

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図1 市区町村データによる乳がん検診受診率 (ベイズ推定・横軸) と乳がん死亡 (EBSMR・縦軸) との関連

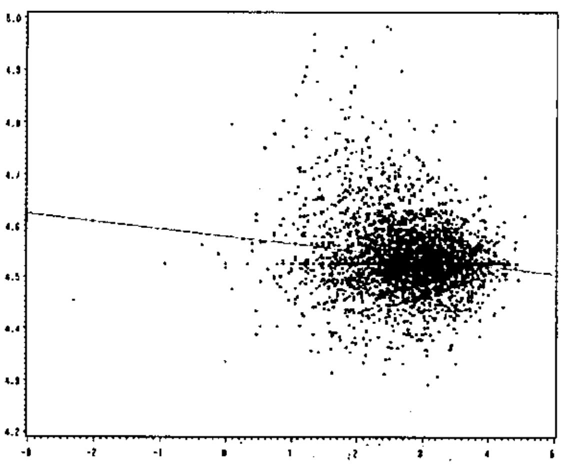


図 2 市区町村データによる子宮がん検診受診率 (ベイズ推定・横軸) と子宮がん死亡 (EBSMR・縦軸) との関連

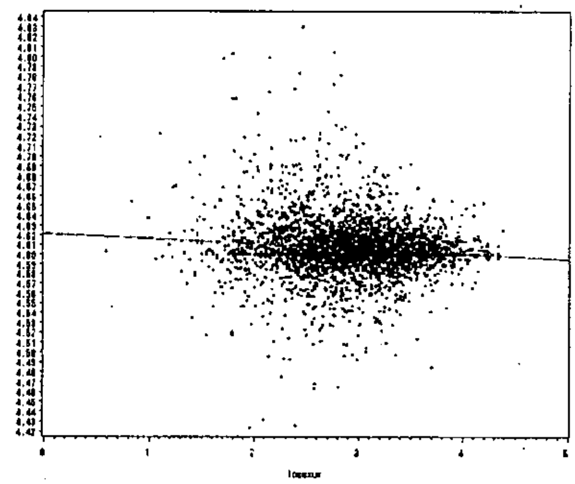
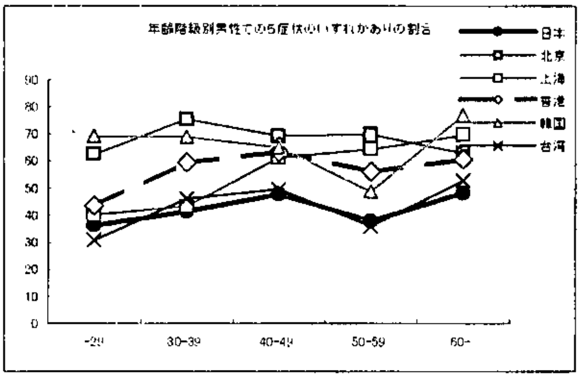


図3　自覚症状5項目にいずれかありとした者の国別年齢階級別割合（左：男性、右：女性）



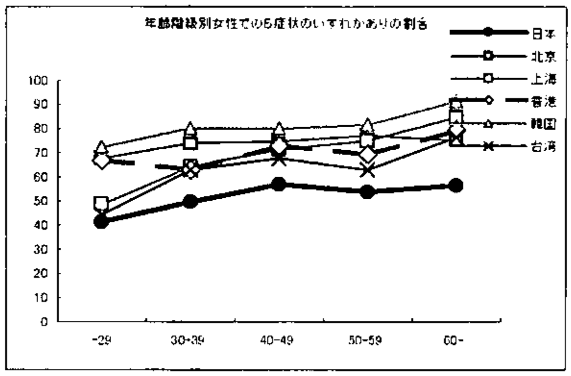
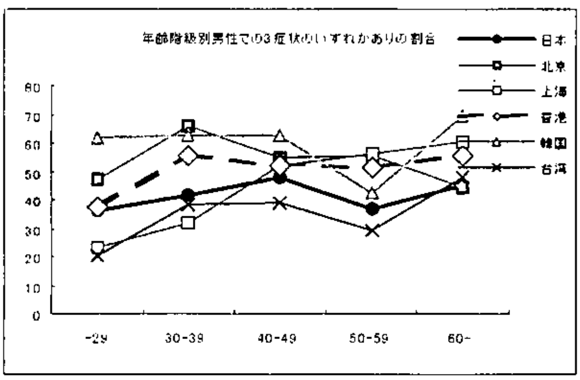


図4　自覚症状3項目にいずれかありとした者の国別年齢階級別割合（左：男性、右：女性）



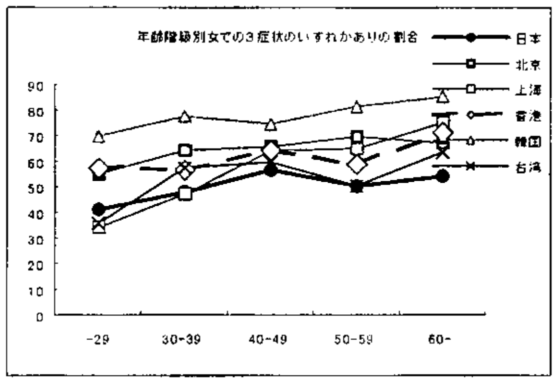
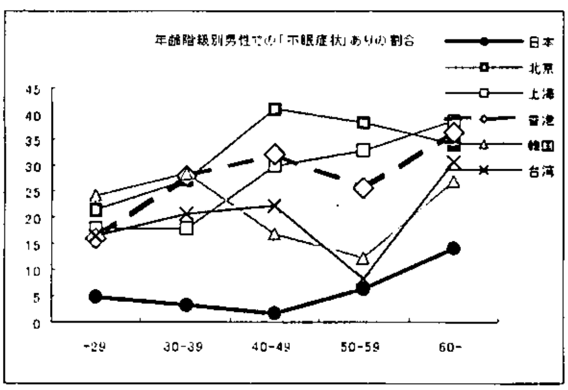
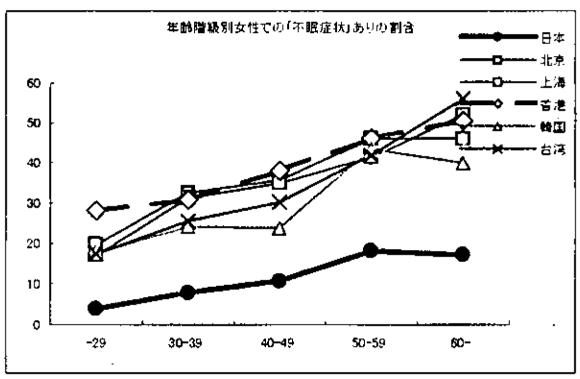


図5　不眠の訴えありとした者の国別年齢階級別割合（左：男性、右：女性）





報告書

女性高脂血症患者の生活習慣病のリスクについて

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研究要旨：高脂血症で外来通院中の患者を対象に、生活習慣病の背景とその動脈硬化症へのリスクを男性と比較・検討した。女性は男性に比較して喫煙率は低いものの、喫煙を継続している割合が高いことが判明した。また高血圧，糖尿病，高脂血症などの生活習慣病は女性は男性より3一5年遅く指摘されていた。またこの3年間で血清脂質をさらに厳格にコントロールする傾向にあることが判明した。しかし虚血性疾患の発症者数はむしろ女性の方が多かった。

A.　研究目的

女性は男性に比較して動脈硬化症の危険度が低いと考えられている。しかし危険因子が蓄積したメタボリックシンドロームなどの病態で、女性の動脈硬化性疾患のリスクがどうなっているのかを検討した結果は少ない。今回高脂血症で外来受診中の女性を対象に、動脈硬化リスクや疾患の発症を男性と比較した。また3年間の血清脂質の変動や動脈硬化性疾患の発症を調査した。

B.　研究方法

当院内科外来に通院中の高脂血症患者（男性159名：女性185名）を対象に解析検討した。

（倫理面への配慮）

対象患者より文書で参加の同意を取得した。

C.　研究結果

女性対象者の年齢は 61.2±11.8 歳で男性の 57.9±10.1 歳と差は認め

られなかった。定期的に運動する習慣を有している割合も男性 38.4%女性 36.8%とほぼ同じであった。喫煙率は男性 33.3%女性 16.8%と女性で低値であった。しかし喫煙経験がある者のうち禁煙した者の割合は、男性で 58.6%と過半数いたのに対し、女性では 40.4%と低値であり、女性の喫煙者の禁煙率は低いことが判明した。定期的にアルコールを飲用する割合は女性では 5.9%と男性の 40.3%に比して明らかに低値であった

現在の BMI は女性では 23.9±3.7 と男性の 25.2±9.4 に比して低値であったが、20 歳時の体重からの増加は女性の方がやや多い傾向にあった。また高血圧，糖尿病，高脂血症の治療を受けている者を対象に診断された年齢を検討したところ、女性は男性より 3ー5 歳ほど高齢で診断を受けていることが明らかになった。女性における高脂血症の診断及び治療開始平均年齢は各々50.6 歳と 52.5 歳であった。

対象女性の調査時の血清総コレステロール，中性脂肪，HDL コレステロール値は各々 224.8±35.3，151.9±112.2，57.1+16.2mg/dl であり、コレステロール，中性脂肪は 3 年前より低下していた。この傾向は男性も同様であった。またこの 3 年間に高脂血症の薬物療法を受けている患者の割合は 63%から 80%に増加していた（図）。

この 3 年間で新たに心血管障害を発症した患者は男性で 1 例であったのに対して女性では 3 例であった。その内訳は狭心症 2 例心筋梗塞 1 例であった。虚血性脳血管障害（脳梗塞）を発症した患者は男性 4 例女性 6 例であった。

D. 考察・結論

外来通院中の高脂血症患者を対象に調査した結果、年齢・運動などの患者背景には男女での差は認められなかった。女性の喫煙率は男性より低値であったがその差は予想ほど大きくなく、また女性では禁煙割合が男性に比較して低いことが判明した。

高血圧，糖尿病，高脂血症といった生活習慣病の発症は女性では男性より 3ー5 年遅れる傾向にあることが判明した。また高脂血症患者の血清脂質値は 3 年前に比較して低下し

ていたが、これは薬物治療を受けている患者割合が増加したためと考えられ、より積極的に高脂血症治療がおこなわれるようになっていることが推測された。

この3年間の検討では、女性は男性と同等かそれ以上の動脈硬化性疾患発症頻度を示していた。

図　血清脂質と薬物療法の変遷

		女性		男性	
		調査時	3年前	調査時	3年前
総コレステロール(mg/dl)		224.8±35.3	231.1±40.3	213.5±34.8	221.2±44.1
HDL コレステロール(mg/dl)		57.1±16.3	57.3±15.7	49.1±13.3	47.7±11.9
中性脂肪(mg/dl)		151.9±112.2	168.7±213.8	184.3±115.7	207.1±169.0
高脂血症薬物療法(%)	有	80	63	68	50
	無	20	37	32	50