TABLE 3. Comparison of variables between wild-type and mutation alleles in CCKAR G-81T and A-128G genotypes

	CCKAR G-128T			CCKAR A-81 G		
	Wild type GG	Mutation GT or TT	p*	Wild type AA	Mutation AG or GG	p
n	1650	601		1317	333	
Age (years)	59.2 ± 0.3†	59.3 ± 0.4	NS‡	59.1 ± 0.3	59.5 ± 0.4	NS
Weight (kg)	57.5 ± 0.2	57.0 ± 0.4	NS	57.6 ± 0.3	57.0 ± 0.3	NS
BMI (kg/m^2)	22.9 ± 0.1	22.9 ± 0.1	NS	22.9 ± 0.1	22.9 ± 0.1	NS
Annual income (%; 54,000 US$ or over)	57.5	58.3	NS	58.3	57.0	NS
Education (%; college or over)	26.9	26.0	NS	27.4	25.6	0.009
Smoking (%; smoker)	22.8	22.8	NS	23.6	21.8	NS
JWAIS-R-SF						
IQ	103.4 ± 0.3	101.6 ± 0.6	0.008	103.6 ± 0.4	102.0 ± 0.5	0.011
Information	9.9 ± 0.1	9.7 ± 0.1	NS	9.9 ± 0.1	9.8 ± 0.1	NS
Picture Completion	10.2 ± 0.1	10.0 ± 0.1	NS	10.2 ± 0.1	10.0 ± 0.1	0.043
Similarities	10.3 ± 0.1	10.1 ± 0.1	NS	10.3 ± 0.1	10.1 ± 0.1	0.051
Digit Symbol	11.7 ± 0.1	11.3 ± 0.1	0.003	11.7 ± 0.1	11.4 ± 0.1	0.008

†Mean ± SE.
‡NS = not significant.
*p-value tested by the t-test or χ^2 test.

genotypes. The IQ levels of subjects with wild-type and mutation alleles at nucleotide -128 were 104.1 ± 0.4 and 102.0 ± 0.6, respectively. There was a significant difference in IQ ($p = 0.002$). The scores of Information and Digit Symbol were significantly lower in subjects with a mutation ($p = 0.012$ and $p = 0.003$, respectively). There were no differences in the scores of Picture Completion and Similarities subtests for polymorphism G-128T. The IQ level was 104.2 ± 0.4 in the subjects with wild-type and 102.6 ± 0.5 in the subjects with mutation at nucleotide -81. Difference in IQ by A-81G polymorphism was significant ($p = 0.008$). Similarities and Digit Symbol subtest scores were significantly lower in subjects with the mutation ($p = 0.033$ and $p = 0.013$, respectively). The Information subtest score was marginally lower with mutation of nucleotide -81 ($p = 0.078$). However, there was no significant difference in the score of Picture Completion subtest.

Haplotype Analysis

Possible haplotypes in the combinations of polymorphism A-81G/G-128T were GA, GG, TG, and TA. However, there were no subjects with AA/GT, AA/TT, or AG/TT genotypic combinations (Table 2). The common haplotype of AA/GT, AA/TT, or AG/TT genotypic combinations was TA. It was considered that no subject had a TA haplotype. The distribution of haplotypes GA, GG, and TG is shown in Table 5. The number of GA haplotypes was 3432; GG was 420; and TG was 650. There was a significant difference in IQ among haplotypes GA, GG, and TG. The IQ for haplotype GA was the highest and the IQ for haplotype TG was the lowest. With an increase in the number of mutation alleles, the IQ level decreased ($p = 0.018$). Digit Symbol scores also significantly decreased with an increasing number of mutation alleles ($p = 0.012$).

TABLE 4. Comparison of intelligences between wild-type and mutation alleles in CCKAR G-81T and A-128G genotypes. Subjects who had used drugs acting on the CNS or subjects with IQ less than 70 were excluded

	CCKAR G-128T			CCKAR A-81G		
	Wild type GG	Mutation GT or TT	p*	Wild type AA	Mutation AG or GG	p
n	1489	539		1178	850	
JWAIS-R-SF						
IQ	104.1 ± 0.4†	102.0 ± 0.6	0.002	104.2 ± 0.4	102.6 ± 0.5	0.008
Information	10.0 ± 0.1	9.6 ± 0.1	0.012	10.0 ± 0.1	9.8 ± 0.1	0.078
Picture Completion	10.2 ± 0.1	10.1 ± 0.1	NS‡	10.3 ± 0.1	10.1 ± 0.1	NS
Similarities	10.4 ± 0.1	10.2 ± 0.1	NS	10.4 ± 0.1	10.2 ± 0.1	0.033
Digit Symbol	11.8 ± 0.1	11.4 ± 0.1	0.003	11.8 ± 0.1	11.5 ± 0.1	0.013

†Mean ± SE.
‡NS = not significant.
*p-value tested by the t-test.

AEP Vol. 15, No. 3
March 2005: 196–201

TABLE 5. Comparison of intelligences between wild-type and mutation alleles in CCKAR G-81T and A-128G genotypes

	Haplotype			
	GA	GG	TG	p for trend*
n	3432	420	650	
JWAIS-R-SF				
IQ	103.2 ± 0.2†	103.0 ± 0.7	101.7 ± 0.6	0.018
Information	10.0 ± 0.1	9.8 ± 0.1	9.7 ± 0.1	NS‡
Picture Completion	10.2 ± 0.1	10.1 ± 0.1	10.0 ± 0.1	NS
Similarities	10.3 ± 0.1	10.1 ± 0.1	10.1 ± 0.1	NS
Digit symbol	11.6 ± 0.1	11.6 ± 0.1	11.3 ± 0.1	0.012

†Mean ± SE.
‡NS = not significant.
*Trend of the three groups was tested by the general linear model.

DISCUSSION

Accumulating data support the involvement of the dopaminergic system in cognitive processing. It is known that CCKAR modulates CCK-stimulated dopamine release in the brain, and mutations in the CCKAR gene may influence the dopaminergic system (5). Considerable preclinical and clinical evidence indicate that inhibitory effects on dopaminergic systems by antipsychotic medications may account for cognitive impairment. A report showed sustained activation of the human mesolimbic dopaminergic system during the performance of cognitive tasks (13). It was also reported that systemic administration of the CCKAR selective antagonist, devazepide, impaired the development of conditioned incentive learning in rats (14). From these data, it is suspected that mutation in the CCKAR gene may influence intelligence.

The CCKAR promoter genotypes were significantly related to IQ. The IQ levels of subjects with the mutant allele were significantly lower than those of subjects with the wild-type allele both for G-128T and A-81G genotypes. A difference in IQ by CCKAR promoter gene polymorphisms was seen in both middle-aged and elderly people. In analyses excluding the subjects who had used drugs acting on the CNS and subjects with IQ less than 70, there was also a significant difference in IQ between the wild and mutation genotypes. We carried out association studies of quantitative traits with haplotypes, and found that the IQ became lower with an increase in the number of mutation alleles.

The CCKAR gene polymorphisms of G-128T and A-81G are located in the promoter region of the gene. It is suspected that mutation of these genotypes is related to the amount of CCKAR production. However, it is still unclear whether these CCKAR polymorphisms are functional or if they are in linkage disequilibrium with other as yet unknown polymorphisms in the CCKAR gene or in a neighboring gene.

In the studies on intelligence in the general population, investigation of genetic factors is an important issue (15). However, at the present time, gene polymorphism has infrequently been reported to be associated with cognition (16). It is suspected that there are many genes associated with individual differences in intelligence, and intelligence is determined from interactions of these gene polymorphisms. However, the contribution of each gene to intelligence may be small as indicated by the results of this study. Testing of thousands of subjects is required to detect small but significant differences. A detailed assessment of IQ requires interviews by psychologists. Assessment of IQ in a large-scale community-dwelling population is generally difficult. It is also difficult to obtain DNA specimens from community-dwelling populations. Because of this, studies on the association between genotype and intelligence have not progressed. In the present study, we showed the relationship between intelligence and CCKAR promoter mutations G-128T and A-81G in community-living middle-aged and elderly Japanese. CCKAR-promoter genotyping may provide useful information for assessing intelligence and preventing cognitive impairment.

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Association of a −1997G → T Polymorphism of the Collagen Iα1 Gene with Bone Mineral Density in Postmenopausal Japanese Women

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Abstract Genetic variants that affect collagen Iα1 metabolism may be important in the development of osteoporosis or osteoporotic fractures. A −1997G → T polymorphism in the promoter of the collagen Iα1 gene (COL1A1) was shown to be associated with bone mineral density (BMD) for the lumbar spine in postmenopausal Spanish women. The relation of this polymorphism to BMD in Japanese women or men has now been examined in a population-based study. The subjects (1,110 women, 1,126 men) were 40 to 79 years of age and were randomly recruited for a population-based prospective cohort study of aging and age-related diseases. BMD for the lumbar spine, right femoral neck, right trochanter, and right Ward's triangle was measured using dual-energy x-ray absorptiometry. Genotypes for the −1997G → T polymorphism of COL1A1 were determined with a fluorescence-based allele-specific DNA primer assay system. When all women were analyzed together, BMD for the lumbar spine and trochanter was significantly lower in subjects with the *COL1A1*G/*G* genotype than in those in the combined group of *COL1A1*G/*T* and *COL1A1*T/*T* genotypes. When postmenopausal women were analyzed separately, BMD for the femoral neck and trochanter was also significantly lower in those with the *COL1A1*G/*G* genotype than in those with the *COL1A1*G/*T* genotype or those in the combined group of *COL1A1*G/*T* and *COL1A1*T/*T* genotypes. BMD was not associated with −1997G → T genotype in premenopausal women or in men. Multivariate regression analysis revealed that −1997G → T genotype affected BMD at various sites with a variance of 0.46–0.62% for all women and 0.61–1.01% for postmenopausal women. The −1997G → T genotype was not related to the serum concentration of osteocalcin, the serum activity of bone-specific alkaline phosphatase, or the urinary excretion of deoxypyridinoline or cross-linked N-telopeptides of type I collagen in men or in premenopausal or postmenopausal women. These results suggest that COL1A1 is a susceptibility locus for reduced BMD in postmenopausal Japanese women.

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Osteoporosis, a major health problem of the elderly, is characterized by a reduction in bone mineral density (BMD) and a deterioration in the microarchitecture of bone, both of which result in predisposition to fractures (Kanis et al. 1994). Although several environmental factors, including diet, smoking, and physical exercise, influence BMD, a genetic contribution to this parameter has been recognized (Peacock et al. 2002). Genetic linkage analyses (Morrison et al. 1994; Johnson et al. 1997; Devoto et al. 1998; Koller et al. 1998, 2000; Niu et al. 1999) and candidate gene association studies (Morrison et al. 1994; Kobayashi et al. 1996; Uitterlinden et al. 1998; Yamada et al. 2001; Ishida et al. 2003) have implicated several loci and candidate genes in the regulation of bone mass and the prevalence of osteoporosis or osteoporotic fractures. However, the genes that contribute to genetic susceptibility to osteoporosis remain to be identified definitively.

Type I collagen is the most abundant protein of bone matrix. Mutations in the coding regions of the genes for the two type I collagen chains (COL1A1 and COL1A2) result in a severe autosomal dominant pediatric condition known as osteogenesis imperfecta (Sykes 1990). A G → T single nucleotide polymorphism (SNP) at the first base of a consensus binding site for the transcription factor Sp1 in the first intron of COL1A1 was associated not only with BMD in white women (Grant et al. 1996) but also with osteoporotic fractures in postmenopausal women (Langdahl et al. 1998; Uitterlinden et al. 1998). The *COL1A1*T* allele of this polymorphism affects collagen gene regulation in such a manner that it increases the production of the α1(I) collagen chain relative to that of the α2(I) chain and leads to reduced bone strength by a mechanism that is partly independent of bone mass (Mann et al. 2001). These observations thus implicate genetic variants that affect collagen Iα1 metabolism as important determinants of the development of osteoporosis and osteoporotic fractures. Other studies, however, have shown only a weak association of the Sp1 binding site polymorphism with BMD or osteoporotic fractures in premenopausal French women (Garnero et al. 1998) or a lack of association in postmenopausal women in Sweden (Liden et al. 1998), in American women (Hustmyer et al. 1999), or in postmenopausal Danish women (Heegaard et al. 2000).

A −1997G → T SNP in the promoter of COL1A1 was also associated with BMD for the lumbar spine in postmenopausal Spanish women, and this SNP and the G → T SNP of the Sp1 binding site of COL1A1 were shown to be in linkage disequilibrium (Garcia-Giralt et al. 2002). Given the ethnic divergence of gene polymorphisms, it is important to examine polymorphisms potentially related to BMD in each ethnic group. We have now examined whether the −1997G → T SNP of COL1A1 is associated with BMD in Japanese women or men in a population-based study.

Materials and Methods

Study Population. The National Institute for Longevity Sciences Longitudinal Study of Aging (NILS-LSA) is a population-based prospective cohort study

of aging and age-related diseases (Shimokata et al. 2000). The subjects of the NILS-LSA are stratified by both age and sex and are randomly selected from resident registrations in the city of Obu and the town of Higashiura in central Japan (Yamada et al. 2003a, 2003b). Individuals with disorders known to cause abnormalities of bone metabolism, including diabetes mellitus, renal diseases, rheumatoid arthritis, and thyroid, parathyroid, and other endocrinologic diseases, were excluded from the study. Women who had taken drugs such as estrogen, progesterone, glucocorticoids, and bisphosphonates were also excluded.

We examined the relation of BMD at various sites to the −1997G → T SNP of COL1A1 in 2,236 participants (1,110 women, 1,126 men). All analyses were performed separately for men and for women. In addition, to uncover potential differences between women according to menopausal status, we conducted all analyses separately for premenopausal and postmenopausal women. Menopausal status was evaluated by a detailed questionnaire, and menopause was defined as complete cessation of menstruation. Furthermore, the relation of biochemical markers of bone turnover to −1997G → T genotype of COL1A1 was examined for men or premenopausal or postmenopausal women separately. The study protocol was approved by the Committee on Ethics of Human Research of National Chubu Hospital and the NILS, and written informed consent was obtained from each subject.

Measurement of BMD. BMD for the lumbar spine (L2–L4), right femoral neck, right trochanter, and right Ward's triangle was measured using dual-energy x-ray absorptiometry (DXA) (QDR 4500; Hologic, Bedford, Mass.). The coefficients of variation (CVs) of the DXA instrument were 0.9% (L2–L4), 1.3% (femoral neck), 1.0% (trochanter), and 2.5% (Ward's triangle); these values were determined by measurement of BMD three times at each site in 10 healthy subjects (mean age ± SE, 38.7 ± 2.4 years).

Determination of Genotypes. Genotypes were determined with a fluorescence-based allele-specific DNA primer assay system (Toyobo Gene Analysis, Tsuruga, Japan) (Yamada et al. 2002). The polymorphic region of COL1A1 was amplified using the polymerase chain reaction with allele-specific sense primers labeled at the 5′ end with either fluorescein isothiocyanate (5′-TGGGTCAGTTCCAAGAGXCC-3′) or Texas red (5′-TGGGTCAGTTCCAAGAGXAC-3′) and with an antisense primer labeled at the 5′ end with biotin (5′-TCTAAATGTCTGTTCCCTCCAA-3′). The reaction mixture (25 μL) contained 20 ng of DNA, 5 pmol of each primer, 0.2 mmol/L of each deoxynucleoside triphosphate, 3.5 mmol/L $MgCl_2$, and 1 U of rTaq DNA polymerase (Toyobo, Osaka, Japan) in polymerase buffer. The amplification protocol was initial denaturation at 95°C for 5 min; 35 cycles of denaturation at 95°C for 30 s, annealing at 60°C for 30 s, and extension at 68°C for 30 s; and a final extension at 68°C for 2 min.

The amplified DNA was incubated in a solution containing streptavidin-conjugated magnetic beads in the wells of a 96-well plate at room temperature.

The plate was then placed on a magnetic stand, and the supernatants from each well were transferred to the wells of a 96-well plate containing 0.01 mol/L NaOH and measured for fluorescence with a microplate reader (Fluoroscan Ascent; Dainippon Pharmaceutical, Osaka, Japan) at excitation and emission wavelengths of 485 nm and 538 nm, respectively, for fluorescein isothiocyanate and of 584 nm and 612 nm, respectively, for Texas red.

Measurement of Biochemical Markers of Bone Turnover. Venous blood and urine samples were collected in the early morning after the subjects had fasted overnight. Blood samples were centrifuged at 1,600 × *g* for 15 min at 4°C, and the serum fraction was separated and stored at −80°C until analysis. The serum concentration of intact osteocalcin was measured with an immunoradiometric assay kit (Mitsubishi Chemical, Tokyo, Japan). The activity of bone-specific alkaline phosphatase in serum was measured with an enzyme immunoassay kit (Metra Biosystems, Mountain View, Calif.). Urine samples were collected in plain tubes and stored at −80°C. Urinary deoxypyridinoline was measured with an enzyme immunoassay kit (Metra Biosystems); the values were corrected for urinary creatinine and expressed as picomoles per micromole of creatinine. The urinary concentration of cross-linked N-telopeptides of type I collagen (NTx) was measured with an enzyme-linked immunosorbent assay kit (Mochida Pharmaceutical, Tokyo, Japan); the values were expressed as picomoles of bone collagen equivalents per micromole of creatinine. Urinary creatinine was enzymatically measured with a creatinine test kit (Wako Chemical, Osaka, Japan).

Statistical Analysis. Quantitative data were compared among the three groups using one-way analysis of variance and the Tukey-Kramer post hoc test and between two groups using the unpaired Student's *t* test. BMD values were analyzed with adjustment for age and body mass index (BMI) using the least-squares method in a general linear model. The effect of −1997G → T genotype on BMD at various sites was evaluated using multivariate regression analysis; R^2 and *P* values were calculated from the analysis including age, BMI, and COL1A1 genotype (0 = *COL1A1*G/*G*, 1 = *COL1A1*G/*T* = *COL1A1*T/*T*) . Allele frequencies were estimated using the gene-counting method, and the chi-square test was used to identify significant departure from Hardy-Weinberg equilibrium. A *P* value less than 0.05 was considered statistically significant.

Results

The distribution of −1997G → T genotypes was in Hardy-Weinberg equilibrium, and age and BMI did not differ among genotypes for all women (Table 1). BMD for the lumbar spine and trochanter was significantly lower in women with the **G/*G* genotype than in those in the combined group of **G/*T* and

Table 1. BMD and Other Characteristics of All Women (n = 1,110) According to the −1997G → T Genotype of COL1A1

Characteristic	**G/*G*	**G/*T*	**T/*T*	**G/* T + *T/*T*
Number (%)	407 (36.7)	526 (47.4)	177 (15.9)	703 (63.3)
Age (years)	60.0 ± 0.5	58.9 ± 0.5	58.4 ± 0.8	58.8 ± 0.4
BMI (kg/m^2)	22.9 ± 0.2	22.8 ± 0.1	23.0 ± 0.2	22.9 ± 0.1
BMD values (g/cm^2)				
L2–L4	0.855 ± 0.006	0.870 ± 0.006	0.878 ± 0.010	0.872 ± 0.005[a]
Femoral neck	0.672 ± 0.004	0.681 ± 0.004	0.680 ± 0.007	0.681 ± 0.003
Trochanter	0.564 ± 0.004	0.575 ± 0.004	0.574 ± 0.006	0.575 ± 0.003[b]
Ward's triangle	0.500 ± 0.006	0.512 ± 0.005	0.508 ± 0.009	0.511 ± 0.004

Data are means ± SE. BMD values are adjusted for age and BMI.
a. P = 0.039 vs. **G/*G*.
b. P = 0.033 versus **G/*G*.

**T/*T* genotypes; the difference in BMD between the **G/*G* genotype and the combined group of **G/*T* and **T/*T* genotypes (expressed as a percentage of the corresponding larger value) was 1.9% for both the lumbar spine and the trochanter.

We also analyzed BMD and other characteristics for premenopausal and postmenopausal women independently. The distributions of −1997G → T genotypes were in Hardy-Weinberg equilibrium, and age and BMI did not differ among genotypes for premenopausal or postmenopausal women (Table 2). For postmenopausal women there was no difference in years after menopause among genotypes. For premenopausal women BMD was not associated with −1997G → T genotype. In contrast, BMD for the femoral neck or trochanter was significantly lower in postmenopausal women with the **G/*G* genotype than in those with the **G/*T* genotype or those in the combined group of **G/*T* and **T/*T* genotypes; the differences in BMD between the **G/*G* genotype and the combined group of **G/*T* and **T/*T* genotypes were 2.5% for the femoral neck and 2.2% for the trochanter.

The distribution of −1997G → T genotypes was in Hardy-Weinberg equilibrium, but BMD did not differ among these genotypes in men (Table 3).

The effect of −1997G→T genotype on BMD was evaluated using multivariate regression analysis (Table 4). The analysis revealed that the −1997G → T genotype affected BMD at various sites with a variance of 0.46–0.62% for all women and of 0.61–1.01% for postmenopausal women.

The relation of biochemical markers of bone turnover to −1997G → T genotype of COL1A1 was also examined. No association of −1997G → T genotype with the serum concentration of intact osteocalcin, serum activity of bone-specific alkaline phosphatase, or urinary excretion of deoxypyridinoline or NTx was apparent for men or premenopausal or postmenopausal women (Table 5).

11214$ $CH3 01-04-05 13:53:56 PS PAGE 31

Table 2. BMD and Other Characteristics of Women (n = 1,093) According to Menopausal Status and the −1997G → T Genotype of COL1A1

	Premenopausal Women (n = 278)				*Postmenopausal Women* (n = 815)			
Characteristic	**G/*G*	**G/*T*	**T/*T*	**G/*T + *T/*T*	**G/*G*	**G/*T*	**T/*T*	**G/*T + *T/*T*
Number (%)	94 (33.8)	140 (50.4)	44 (15.8)	184 (66.2)	306 (37.5)	377 (46.3)	132 (16.2)	509 (62.5)
Age (years)	45.9 ± 0.4	46.3 ± 0.4	45.8 ± 0.6	46.2 ± 0.3	64.6 ± 0.5	63.8 ± 0.4	62.8 ± 0.7	63.5 ± 0.4
Years after menopause					15.4 ± 0.5	15.1 ± 0.5	13.7 ± 0.8	14.7 ± 0.4
BMI (kg/m^2)	22.8 ± 0.3	22.9 ± 0.3	22.4 ± 0.5	22.8 ± 0.2	23.0 ± 0.2	22.8 ± 0.2	23.2 ± 0.3	22.9 ± 0.1
BMD values (g/cm^2)								
L2–L4	1.018 ± 0.012	1.026 ± 0.010	1.044 ± 0.018	1.030 ± 0.009	0.798 ± 0.007	0.813 ± 0.007	0.821 ± 0.011	0.815 ± 0.006
Femoral neck	0.782 ± 0.009	0.767 ± 0.008	0.771 ± 0.014	0.768 ± 0.007	0.634 ± 0.005	0.650 ± 0.004[a]	0.647 ± 0.007	0.650 ± 0.004[b]
Trochanter	0.656 ± 0.009	0.661 ± 0.007	0.656 ± 0.013	0.660 ± 0.006	0.532 ± 0.005	0.544 ± 0.004	0.545 ± 0.007	0.544 ± 0.004[c]
Ward's triangle	0.663 ± 0.012	0.657 ± 0.010	0.658 ± 0.018	0.657 ± 0.009	0.444 ± 0.007	0.459 ± 0.006	0.455 ± 0.010	0.458 ± 0.005

Data are means ± SE. BMD values are adjusted for age and BMI.

a. P = 0.034 vs. **G/*G*.

b. P = 0.011 vs. **G/*G*.

c. P = 0.033 vs. **G/*G*.

Table 3. BMD and Other Characteristics of Men ($n = 1,126$) According to the −1997G → T Genotype of COL1A1

Characteristic	**G/*G*	**G/*T*	**T/*T**	*G/*T + *T/*T*
Number (%)	457 (40.6)	511 (45.4)	158 (14.0)	669 (59.4)
Age (years)	58.5 ± 0.5	59.7 ± 0.5	59.2 ± 0.9	59.6 ± 0.4
BMI (kg/m^2)	22.9 ± 0.1	23.0 ± 0.1	22.9 ± 0.2	22.9 ± 0.1
BMD values (g/cm^2)				
L2–L4	0.990 ± 0.007	0.975 ± 0.007	0.983 ± 0.012	0.977 ± 0.006
Femoral neck	0.754 ± 0.005	0.754 ± 0.004	0.744 ± 0.008	0.751 ± 0.004
Trochanter	0.672 ± 0.005	0.665 ± 0.004	0.667 ± 0.008	0.665 ± 0.004
Ward's triangle	0.557 ± 0.006	0.552 ± 0.005	0.540 ± 0.010	0.549 ± 0.005

Data are means ± SE. BMD values are adjusted for age and BMI.

Discussion

The −1997G → T SNP of the COL1A1 promoter has previously been associated with BMD for the lumbar spine and, to a lesser extent, with BMD for the femoral neck in postmenopausal Spanish women, and with the **T/*T* genotype, which represents a risk factor for reduced BMD (Garcia-Giralt et al. 2002). We have now shown that the −1997G → T SNP is associated with BMD for the femoral neck and trochanter in postmenopausal Japanese women and with the **G/*G* genotype, which represents a risk factor for reduced BMD. The −1997G → T genotype affected BMD at various sites with a variance of 0.61–1.01% for postmenopausal women, although this SNP was not associated with biochemical markers of bone turnover.

The alleles of the −1997G → T polymorphism associated with reduced

Table 4. Effects of the −1997G → T Genotype of COL1A1 on BMD for All Women ($n = 1,110$) or Postmenopausal Women ($n = 815$)

Site	R^2	P
All women		
L2–L4	0.0061	0.0102
Femoral neck	0.0047	0.0243
Trochanter	0.0062	0.0093
Ward's triangle	0.0046	0.0262
Postmenopausal women		
L2–L4	0.0061	0.0263
Femoral neck	0.0101	0.0044
Trochanter	0.0076	0.0137
Ward's triangle	0.0071	0.0172

The R^2 and P values were derived from multivariate regression analysis including age, BMI, and COL1A1 genotype (0 = **G/*G*, 1 = **G/*T* = **T/*T*).

Table 5. Biochemical Markers of Bone Turnover for Women or Men According to the −1997G → T Genotype of COL1A1

Marker	**G/*G*	**G/*T*	**T/*T*
Premenopausal women			
Osteocalcin (ng/mL)	6.35 ± 0.29	6.46 ± 0.24	6.93 ± 0.42
Bone-specific alkaline phosphatase (U/L)	19.6 ± 0.5	20.3 ± 0.5	19.0 ± 0.8
dPyr (pmol/μmol Cr)	5.54 ± 0.15	5.35 ± 0.12	5.50 ± 0.22
NTx (pmol BCE/μmol Cr)	33.5 ± 1.5	33.6 ± 1.3	38.3 ± 2.3
Postmenopausal women			
Osteocalcin (ng/mL)	10.53 ± 0.21	10.30 ± 0.19	10.25 ± 0.32
Bone-specific alkaline phosphatase (U/L)	31.6 ± 0.6	31.5 ± 0.6	30.5 ± 0.9
dPyr (pmol/μmol Cr)	4.08 ± 0.06	4.01 ± 0.05	3.99 ± 0.10
NTx (pmol BCE/μmol Cr)	60.4 ± 1.6	60.2 ± 1.5	59.4 ± 2.5
Men			
Osteocalcin (ng/mL)	7.67 ± 0.11	7.64 ± 0.11	7.64 ± 0.20
Bone-specific alkaline phosphatase (U/L)	26.3 ± 0.4	25.6 ± 0.4	26.2 ± 0.7
dPyr (pmol/μmol Cr)	4.08 ± 0.06	4.01 ± 0.05	3.99 ± 0.10
NTx (pmol BCE/μmol Cr)	36.6 ± 0.7	36.2 ± 0.7	36.4 ± 1.2

Data are means ± SE. dPyr, deoxypyridinoline; Cr, creatinine; NTx, cross-linked N-telopeptides of type I collagen; BCE, bone collagen equivalents.

BMD thus differ between the present study (**G* allele) and the previous study (**T* allele) (Garcia-Giralt et al. 2002). Although the reason for this apparent discrepancy is unclear, there are three major differences between the two studies. First, the subjects were older in our study (mean age of 64 years for postmenopausal women) than in the previous study (mean age, 51 years), and years since menopause were significantly greater in our study (mean, 15.0 years) than in the previous study (mean, 3.6 years). Given that bone resorption markedly increases during 10 years after menopause, genetic effects on BMD might differ between women for short and long time after menopause. Second, the number of subjects in which the association was detected was greater in our study ($n = 815$ for postmenopausal women) than in the previous study ($n = 256$). The results of association studies with small sample sizes are prone to bias compared with those with large sample sizes. Finally, the distribution of −1997G → T genotypes differed significantly ($P < 0.0001$; chi-square test) between our study (postmenopausal women: **G/*G*, 38%; **G/*T*, 46%; **T/*T*, 16%) and the previous study (**G/*G*, 76%; **G/*T*, 22%; **T/*T*, 2%), possibly reflecting the difference in ethnicity. The difference in genetic influences on BMD between different ethnic groups might be attributable, at least in part, to the difference in the distribution of genotypes. It is also possible that the −1997G → T SNP of COL1A1 is in linkage disequilibrium with other polymorphisms of COL1A1 or with polymorphisms of other nearby genes that are actually responsible for the observed association with BMD. Given the multiple comparisons of genotype performed, we cannot completely exclude the possible occurrence of statistical errors such as

false positives, although we observed a significant association of this SNP with BMD at different sites.

Evidence suggests that the −1997G → T SNP of COL1A1 may affect promoter function (Garcia-Giralt et al. 2002). A double-stranded oligonucleotide containing the −1997G → T site bound osteoblast nuclear factors; however, the extent of factor binding was even more pronounced with a single-stranded antisense DNA probe, suggesting the involvement of a protein selective for single-stranded DNA. The extent of factor binding observed with a probe corresponding to the **G* allele was greater than that apparent with a probe based on the **T* allele. The effect of this SNP on COL1A1 transcription, however, remains to be determined.

In conclusion, our present results suggest that the −1997G → T SNP of COL1A1 is associated with BMD for the femoral neck and trochanter in postmenopausal Japanese women and that the alleles associated with reduced BMD differ between postmenopausal Japanese (**G* allele) and Spanish (**T* allele) women, although the contribution of this SNP to bone mass appears relatively small.

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表　代表的な老化の縦断的研究

名称	開始年	調査機関	対象	人数	追跡サイクル	観察開始時対象年齢	特徴
1. Duke Study	1955	Duke大学	地域在住男女	267	2-4年	60～90歳	歴史的縦断研究
2. BLSA (Baltimore Longitudinal Study of Aging)	1958	NIA(国立老化研究所)	米国内ボランティア	1,200	2年	20歳～	包括的老化縦断研究の象徴的存在
3. Normal Aging Study	1963	Boston退役軍人病院	ボストン近郊の退役軍人	2,032	5年	25～75歳	対象者は健常人
4. Rotterdam Study	1990	Erasmus大学	ロッテルダムの地域住民	11,854	2年	55～98歳	神経老年病，心疾患，運動器疾患，眼科疾患を対象
5. 小金井Study	1976	東京都老人総合研究所	東京都小金井市住民	477	5年	69～71歳	日本の縦断研究の草分け的存在，社会・心理面も考慮
6. NILS-LSA (Natinonal Institute for Longevity Scinences-Longitudinal Study of Aging)	1997	国立長寿医療研究センター	愛知県大府市・東浦町住民	2,267	2年	40～79歳	日本で最初の施設型の包括的な老化の縦断研究

であることが判明した．長寿の達成には中年期における血圧のコントロールと，禁煙，肥満とやせの防止，適度の身体活動，規則的な食生活など生活習慣の改善が特に重要と考えられ，また悪性新生物や循環器疾患の一次予防が重要であると考えられた．

〔児玉　和紀〕

加齢研究の方法

縦断的研究

longitudinal study

老化の縦断的研究は，一定期間ごとに同一対象者に同一検査項目を繰り返し行うことによって，加齢による正味の変化の縦断的変動を観察するものである．経時的な追跡を行う縦断的研究は，横断的研究に比べて，結論が出るまでに何年もの期間を要し，調査を継続するための費用や人材の確保も困難を要することが多い．しかし，老化の観察を行うにあたって，横断的観察のみでは多くのバイアスを生じることがあり，加齢による変化を正確にとらえることができない．このため加齢研究には縦断的方法が欠かせない．

疾病のリスクファクターを探ることを目的としたコホート研究と異なり，老化の縦断的研究は同一項目の検査を繰り返し行い，検査値の縦断的変動を観察することに意義がある(図)．このため対象者数は検査値の縦断的変動が有意となる数千人の範囲とし，できるだけ詳細な老化に関連する検査を実施することが望まれる．縦断的変化を検討するためには検査値の精度が要求されるため，多施設での共同研究は困難で，同一施設，同一検査基準の下での長期の観察が必要となる．このため縦断的研究は，世界をみても，その数は限られたものとなっている(表)．

縦断的加齢研究には，横断的手法を縦断的に応用した研究方法もある．連続的横断研究(successive cross-sectional study)は横断的検討を年度ごとに繰り返し，その変化を検討するものである．対象は一般に同一ではなく，母集団から毎回異なる対象者が無作為に選ばれる．国民栄養調査などがこうした方法を採用している．またコホート内患者対照研究(nested case-control study)は，追跡集団の中で発症したケースと，発症しなかったコントロールとの間で

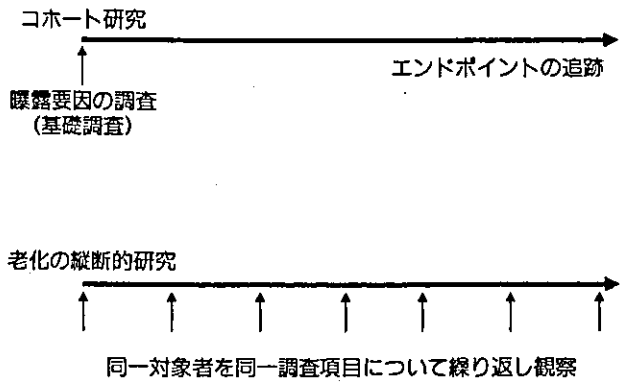

図　コホート研究と老化の縦断的研究

コホート研究では基本的に疾病の曝露要因(循環器疾患では血圧，心電図所見，血清脂質，喫煙歴，心疾患の家族歴など)は初回時にのみ測定され，後はエンドポイント(循環器疾患の発症，死亡など)を追跡する．老化の縦断的研究では老化にかかわる学際的な要因(医学，形態学，栄養学，運動生理学，心理学，社会学的要因)について詳細な検討を繰り返し，同じ精度で行うことが必要である(葛谷文男，下方浩史「老化に関する縦断的研究マニュアル」診断と治療社，1996より一部改変)．

行われる患者対照研究である．

さらに広義の縦断的研究には介入研究[対象集団に何らかの実験的操作(介入)を行って，その結果をみるという研究方法]も含まれる．

老化の縦断的研究は，正常な老化過程の評価の基礎データとして重要であり，主たる意義としては，① Normal Aging や Successful Aging の定量，②個人の縦断的観察による経年的基準値の設定，などがあげられる．さらにこの研究の副次的意義として，①老化に関する疾患の早期マーカーの発見，②長寿要因の解析，③生活習慣・ストレス・ライフイベンツ・疾患などの老化の進行に及ぼす影響の解析，④加齢の病気進行への影響の検討，⑤死亡や疾患・disability のリスクファクターの分析，⑥正常な加齢と加齢が引き金となる疾患の判別，⑦他地域，諸外国との比較，⑧加齢に伴う老年者の社会的，経済的変化の検討，⑨生理学的年齢の指標作成，などをあげることができ，加齢の研究方法としては困難は伴うにしても現在実行しうる最適の方法である．

日本での最初の老化の縦断的調査は東京都老人総合研究所の小金井スタディとそれに続く，中年からの老化予防総合的長期追跡研究(TMIG-LISA)であろう．さらに1997年から国立長寿医療研究センターで開始された「老化に関する長期縦断疫学研究(NILS-LSA)」は専用施設に参加者を招くことによって，頭部 MRI，DXA による骨量・脂肪量測定，三次元動作解析など精度の高い最新の検査を含み，また，医学・分子疫学・形態学・運動生理学・栄養学・心理学分野の調査を含む包括的な老化に関する縦断的疫学調査である．

〔安藤　富士子〕

加齢研究の方法

コホート研究

cohort study

コホート cohort とはローマ時代の百人隊とか，千人隊という部隊の単位である．一定の集団を調査・追跡していき，どのような特徴をもった人がどのような疾患になるのか，その場合，何が原因なのか，ということを解析する疫学研究がコホート研究である．コホート研究は数百人規模の工場内での化学物質への曝露集団を対象に行われることが多かったが，発症率の低いがんのリスクを対象にするような場合には，特定の患者発症数を確保するために10万人以上の住民を対象とした大規模な研究が必要である．発生数を見込んで規模を決める必要がある．

多くの慢性疾患は単一の原因によって起きるものではない．長年の生活習慣の積み重ねで高齢になるとがんや高血圧，心臓病，糖尿病や痛風など，さまざまな慢性疾患に悩まされることになる．逆に，単一の原因が多くの疾患のもとになっている場合もあ

従って，このような国民全体の，あるいは高齢者全体での死亡原因の変動については今後数年を経て安定化するまで注意深く見守る必要がある．

65歳以上あるいは80歳以上の高齢者の死亡原因については，今述べたような全体的な死亡原因とはかなり異なったパターンを示している(図1, 2)．すなわち，高齢者になるほど悪性新生物(がん)による死亡は減少し，かわって心疾患や脳血管障害という循環器疾患によるものが多くなってくる．平成11(1999)年の統計では女性の80歳以上の群では第1位が心疾患(20.2%)，第2位が脳血管疾患(19.1%)であり，これら全死亡の約4割を占めている．さらに高齢期の死亡原因として重要な意味をもつ肺炎(気管支炎を含む)は13.7%で第4位であり，悪性新生物は第3位(15.3%)となっている．

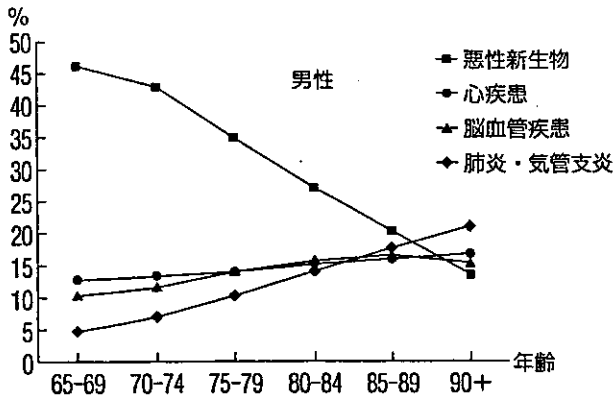

図1　各年齢別4大死亡割合(%)

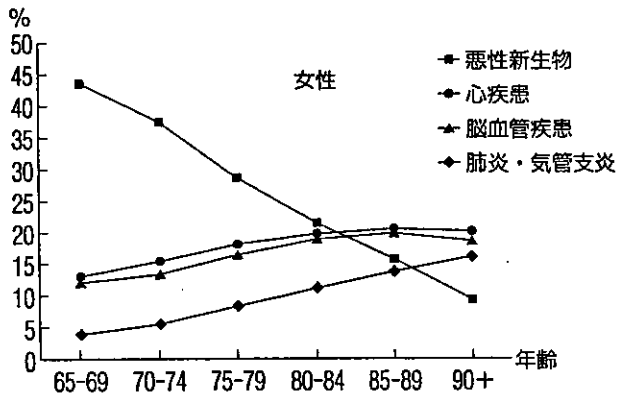

図2　各年齢別4大死亡割合(%)

もう1つの高齢者死亡の特徴は老衰死が死亡原因の高位に位置していることである．平成11年には約2万3000人が老衰で死亡し，65歳以上の死因の第6位となっている他，80歳以上の群では総死亡に占める割合が男性で3.4%，女性で約6.3%となっており，高齢者死因に関する病理学的・臨床的検索が一段と向上した現在にあっても漸減傾向にあるとはいえ，いわゆる老衰とせざるを得ない高齢者死亡が確実に存在している．　〔鈴木　隆雄〕

高齢者の死亡と疾患

疾病と死亡の国際比較

平均寿命の国際比較は国による統計作成基礎期間の違いや統計処理上の問題などがあるが，明らかになっている資料上では日本は世界有数の長寿国である．また，年齢調整死亡率も先進諸国の中で最も低い(表1)．年齢階級別に死亡率を比較してみると表2に示すように日本の乳児死亡率は先進各国の中でも最も低い．1〜4歳の死亡率は諸外国と比較して若干高いものの，以後学童期から老年期に至るまで，年齢別の死亡率は総じて低く，全体として平均寿命を引き上げる要因となっている．これらは民族的・遺伝的要因もさることながら，保健水準の高さおよび食生活をはじめとした環境要因が欧米諸外国に比して優れていることを示していると考えられる．

疾患別の死亡率について先進諸国に関するWHOの統計(1997-1999)と厚生労働省の人口動態統計(1999)などによると
(1)悪性新生物による年齢調整死亡率(人口10万対)は男性ではフランスの213.4をはじめとしてオランダ，イタリア，イギリスなど主にヨーロッパでは日本より高率と

なっている．日本人男性では175.8でアメリカの175.6と大きな差は認められないがスウェーデンの144.8と比べると高値である．日本人女性の111.6はイギリス(130.0)，オランダ(124.4)，アメリカ(121.1)と比較すると低いが，フランス(96.8)よりも高い．日本では男女の胃癌による死亡が欧米諸国と比較するとまだ高く，肺癌や女性の乳癌の死亡率は低い．しかし，その差は年々縮小する傾向にある．

表1　粗死亡率・年齢調整死亡率・乳児死亡率一国際比較

	粗死亡率[1)](人口千対)		年齢調整死亡率[2)](人口千対)		乳児死亡率(出生千対)
	男	女	男	女	
日本('99)	8.7	7.0	5.6	2.9	3.4
カナダ('97)	7.5	6.8	6.3	3.9	5.3
アメリカ合衆国('97)	8.8	8.5	7.2	4.6	7.1
フランス('96)	9.7	8.6	6.7	3.5	4.8
ドイツ('97)	10.0	11.0	7.3	4.3	4.9
オランダ('97)	8.7	8.7	7.0	4.2	*5.2
スウェーデン('96)	10.8	10.5	6.1	3.8	4.0
イギリス('97)	10.4	11.0	7.1	4.6	5.9
オーストラリア('95)	7.4	6.5	6.4	3.9	5.7
ニュージーランド('96)	7.9	7.4	7.1	4.6	7.1

注　1) 粗死亡率は，年齢調整死亡率と併記したので粗死亡率と表したが，単に死亡率といっているものである．
2) 年齢調整死亡率の基準人口は世界人口による．日本も同様であるので表13と異なる．
＊ オランダは暫定値である．
資料　厚生労働省「人口動態統計」
WHO「World Health Statistics Annual 1997～1999」
UN「Demographic Yearbook 1998」
(2001「国民衛生の動向」から)

(2)日本人の心疾患による死亡率120.4はイギリス(291.6)，アメリカ(260.7)，フランス(184.6)と比較して未だにかなり低いものとなっている．

(3)脳血管疾患による年齢調整死亡率は日本人男性では66.9，女性では56.8であり，アメリカ(37.0，32.8)，フランス(39.9，27.9)と比較すると高率であるが，先進欧米諸国の中にもオーストリア(63.7，51.8)，イタリア(62.4，49.9)，ドイツ(60.5，47.0)のように比較的高い国もあり，単なる人種差だけではなく，生活習慣などの影響が大きいと考えられる．

(4)日本の死因の第4位は肺炎および気管支炎であるが，肺炎による死亡率は先進諸外国と比較してかなり高率になっている．

〔安藤　富士子〕

高齢者の死亡と疾患

疾病と死亡の国内比較

1999年の厚生省人口動態統計によれば，全国の死亡総数は982,031人で，粗死亡率は7.8(人口千対)である．都道府県別にみて死亡率が最も高率だったのは島根県の10.8で，ついで高知県，秋田県となっている．一方死亡率が低いのは埼玉県，沖縄県

表2　年齢階級別にみた死亡率(人口10万対)一国際比較

	総数	0歳[1)]	1～4	5～14	15～24	25～34	35～44	45～54	55～64	65～74	75歳以上
日本('99)	782.9	340.5	33.0	13.1	42.6	59.1	115.2	295.8	669.9	1,659.8	6,630.2
カナダ('97)	718.7	552.8	29.0	17.6	60.4	72.4	132.4	303.8	834.7	2,160.1	7,799.2
アメリカ合衆国('97)	864.7	722.6	35.8	20.8	86.2	115.0	203.2	430.8	1,063.6	2,509.7	8,118.4
フランス('96)	917.8	476.8	27.8	15.7	63.0	104.0	194.9	394.3	866.1	1,908.3	8,034.1
ドイツ('97)	1,048.6	486.5	28.2	13.3	57.3	73.8	163.3	399.0	932.0	2,368.7	9,113.9
オランダ('97)	874.3	495.4	28.2	14.7	40.4	59.8	127.6	327.3	871.0	2,378.4	9,085.4
スウェーデン('96)	1,061.1	382.5	19.2	11.0	35.8	60.0	115.3	300.5	748.9	2,083.1	8,497.6
イギリス('97)	1,067.2	586.0	26.5	14.6	53.8	69.9	132.5	339.0	945.5	2,667.9	9,097.0
オーストラリア('95)	692.6	555.8	34.5	17.1	70.1	91.6	131.6	282.9	791.7	2,182.5	7,894.6
ニュージーランド('96)	763.7	726.1	41.9	21.8	95.6	101.4	126.5	352.5	967.5	2,458.2	8,481.7

注　1) 0歳は出生10万対の率である．
資料　厚生労働省「人口動態統計」
WHO「World Health Statistics Annual 1997～1999」
(2001「国民衛生の動向」から)

なっている．日本人男性では175.8でアメリカの175.6と大きな差は認められないがスウェーデンの144.8と比べると高値である．日本人女性の111.6はイギリス(130.0)，オランダ(124.4)，アメリカ(121.1)と比較すると低いが，フランス(96.8)よりも高い．日本では男女の胃癌による死亡が欧米諸国と比較するとまだ高く，肺癌や女性の乳癌の死亡率は低い．しかし，その差は年々縮小する傾向にある．

表1　粗死亡率・年齢調整死亡率・乳児死亡率—国際比較

	粗死亡率[1](人口千対)		年齢調整死亡率[2](人口千対)		乳児死亡率(出生千対)
	男	女	男	女	
日本('99)	8.7	7.0	5.6	2.9	3.4
カナダ('97)	7.5	6.8	6.3	3.9	5.3
アメリカ合衆国('97)	8.8	8.5	7.2	4.6	7.1
フランス('96)	9.7	8.6	6.7	3.5	4.8
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注　1) 粗死亡率は，年齢調整死亡率と併記したので粗死亡率と表したが，単に死亡率といっているものである．
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(2)日本人の心疾患による死亡率120.4はイギリス(291.6)，アメリカ(260.7)，フランス(184.6)と比較して未だにかなり低いものとなっている．
(3)脳血管疾患による年齢調整死亡率は日本人男性では66.9，女性では56.8であり，アメリカ(37.0，32.8)，フランス(39.9，27.9)と比較すると高率であるが，先進欧米諸国の中にもオーストリア(63.7，51.8)，イタリア(62.4，49.9)，ドイツ(60.5，47.0)のように比較的高い国もあり，単なる人種差だけではなく，生活習慣などの影響が大きいと考えられる．
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表2　年齢階級別にみた死亡率(人口10万対)—国際比較

	総数	0歳[1]	1～4	5～14	15～24	25～34	35～44	45～54	55～64	65～74	75歳以上
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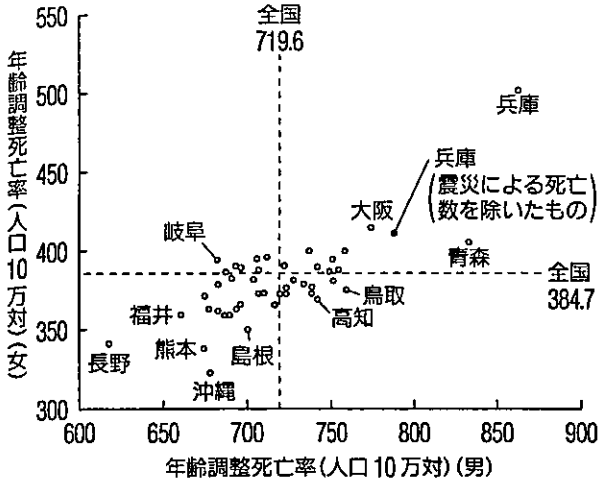

図1　都道府県別年齢調整死亡率(人口10万対)
—男・女—　(2001「国民衛生の動向」から)

の6.0である．しかし各県の年齢別人口構成が異なるので，1995年の年齢調整死亡率(1985年モデル人口を基準人口とする)，(人口10万対)を都道府県別に比較すると(図1)死亡率が低いのは長野県，沖縄県，熊本県，福井県，島根県などであり，死亡率が高いのは兵庫県，青森県，大阪府，和歌山県などである．全ての県で男性の年齢調整死亡率は女性よりも高く，また，男性と女性の死亡率には強い相関が認められる．

1995年の三大死因の都道府県別の年齢調整死亡率(人口10万対)を図2に示す．1997年の調査でもほぼ同等の結果が得られている．

(1)悪性新生物では男性では中部，四国，南九州に低死亡率県が多く，近畿西部，北九州に高死亡率県が多い．女性ではモザイク

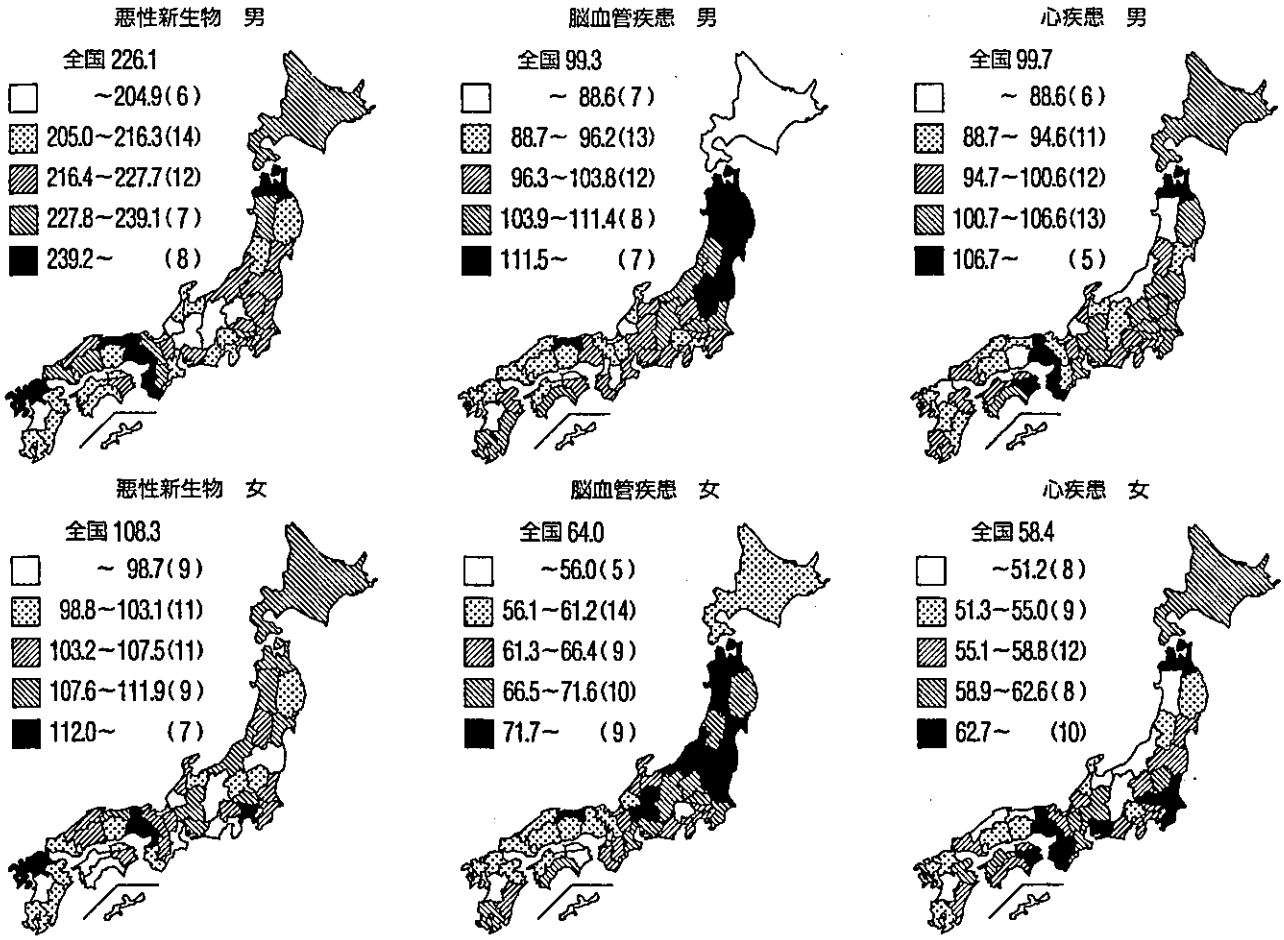

図2　都道府県別にみた年齢調整死亡率(人口10万対)

注　年齢調整死亡率の基準人口は，「昭和60年モデル人口」である．階級分けについては，標準偏差により，5階級に分けている．

資料　厚生省(現・厚生労働省)「平成7年都道府県別年齢調整死亡率」　(2001「国民衛生の動向」から)

状になっており，一定の傾向はつかみにくい．

(2)脳血管疾患では，男女とも西日本に低死亡率県が多く，東北，関東北部など東日本に高死亡率県が集中している．

(3)心疾患では，男女とも日本海側に低死亡率県が多い．高死亡率県は近畿西部，関東北海道などである．

しかし，これらのデータには阪神・淡路大震災(1995年)の影響が大きく反映されていることに考慮が必要である．

〔安藤　富士子〕