A significant decrease in the incidence of vertebral fractures and the safety of the drug were consistently observed during the 5-year treatment with bazedoxifene.

Calcitonin derivatives

Calcitonin is a bone resorption inhibitor acting directly on osteoclasts and pre-osteoclasts to control their functions. Calcitonin also relieves pain via the central serotoninergic system, and therefore its derivatives may be the first choice to obtain pain relief and improves QOL in the early phase after the occurrence of osteoporotic fractures or in patients with postural distortion associated with vertebral fractures.

There are some reports on the effect of calcitonin derivatives on BMD and vertebral fracture (Fig. 13a) [16], but none on non-vertebral or proximal femoral fractures.

Some randomized clinical trials and systematic reviews revealed significant reductions in the severity of pain associated with ADLs 1 to 4 weeks after calcitonin was started (Fig. 13b) [17]. In terms of QOL, improvement in SF-36 scores, pain relief, and improved ADLs, and an enhanced effect of rehabilitation in patients who had a total hip replacement after proximal femoral fracture was reported.

Outside of Japan, intra-nasal formulations of calcitonin derivatives are used primarily, and a preventive effect on fractures and beneficial effect on pain was observed. However, the increased risk of cancer was reported from the European Medical Association (EMA) in patients treated with calcitonin and intra-nasal calcitonin was withdrawn from the European market.

Although antibodies might be produced after injection of calcitonin derivatives, they do not influence the effect of calcitonin and are not involved in the side effects of calcitonin derivatives. Therefore, patient monitoring is not needed.

Teriparatide (recombinant human parathyroid hormone)

Unlike bone-resorption inhibitors, intermittent administration of teriparatide (a recombinant form) as a daily subcutaneous injection specifically increases serum P1NP, a bone formation marker, indicating promotion of bone remodeling followed by the formation of bone tissue.

Teriparatide, given as a daily subcutaneous injection, is recommended in patients at high risk of fractures such as patients who have had a fracture(s) while being treated with a bisphosphonate or SERM, elderly patients with multiple vertebral fractures or proximal femoral fractures, or patients with significantly reduced BMD. The combination of teriparatide with an oral bisphosphonate is not recommended.

Teriparatide increases BMD at the lumbar vertebrae and proximal femur, and reduces vertebral and non-vertebral fracture. The incidence of a radial fracture is reduced with teriparatide, while the apparent BMD of the radius is slightly decreased in association with the formation of new bone matrix, and the external diameter of the radius is increased. A meta-analysis revealed that teriparatide reduces low back pain.

Teriparatide (a recombinant form) approved in Japan is self-injected daily at home, after instruction by physicians or nurses. The total dosing period is limited to 24 months. After 24 months of treatment with teriparatide, adequate treatment with a bone-resorption inhibitor is recommended to maintain the bone strength.

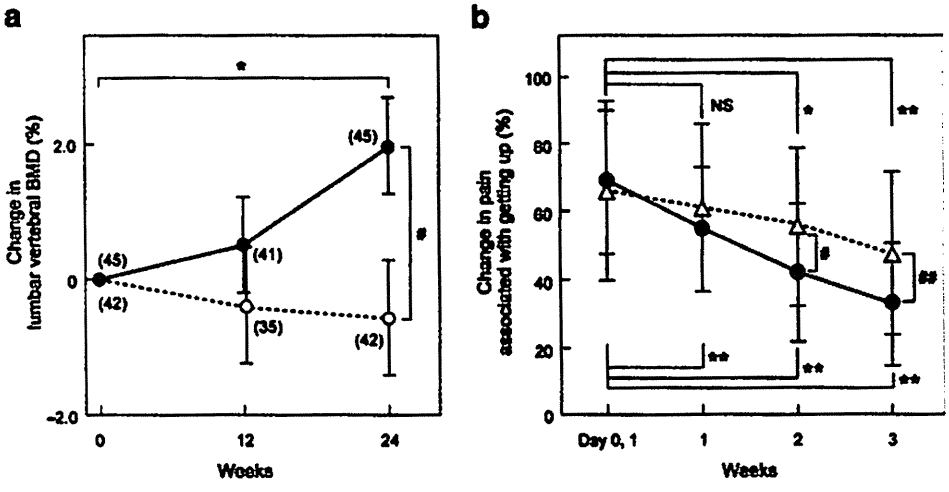

Fig. 13 Effect of elcatonin on BMD and pain associated with vertebral fracture. a Percent change in lumbar spine BMD. *Solid line* is elcatonin (20 units per week) with 0.6 g calcium lactate and *broken line* is control (calcium lactate only). Data are mean ± SE. Numerals in parentheses denote number of patients. Comparison within groups: Student's paired *t*-test, #$p<0.05$; between groups: Student's unpaired *t*-test, *$p<0.05$. Orimo H [16] (Copyright© 1996 Springer Science + Business Media BV). b Percent change in pain associated with getting up evaluated with visual analog scale (*VAS*). *Solid line* is elcatonin (20 units per week, $n=44$) and *broken line* is control (untreated, $n=42$). Two-way repeated-measures ANOVA, *$p<0.05$, **$p<0.01$, *NS* not significant. Mann–Whitney *U* test, #$p<0.05$, ##$p<0.01$ (Nakano [17])

Combination therapy

Osteoporosis is a multifactorial disease, thus combination therapy with agents with different mechanisms of action is considered reasonable. However, the efficacy of combination therapy lacks evidence at this time.

The Adequate Treatment of Osteoporosis (A-TOP) Research Group was authorized in the year 2000 by the Japan Society of Osteoporosis and assisted by the Public Health Research Foundation to obtain clinical evidence regarding osteoporosis treatment. It conducted a clinical trial comparing monotherapy with alendronate, a new bisphosphonate at the time, and combination therapy with alendronate and alfacalcidol, an active vitamin D_3 derivative developed in Japan (Japanese Osteoporosis Intervention Trial: JOINT-02). The incidence of vertebral fracture was significantly reduced in the combination therapy group during the first 6 months of treatment, and in both subgroups of patients with multiple vertebral fractures and grade 3 vertebral fractures by semiquantitative assessment during the 2-year treatment period (Fig. 14) [18]. The incidence of non-vertebral fracture (weight-bearing bones) was also significantly reduced in the combination therapy group. Based on these results, combination therapy with alendronate and an active vitamin D_3 derivative is recommended for the prevention of incident vertebral and non-vertebral fracture in patients at a high risk of fracture.

Secondary osteoporosis

Osteoporosis secondary to other diseases

Secondary osteoporosis is defined as decreased BMD and deteriorated bone quality (pathologic state specific to osteoporosis) having one or more causes in addition to genetic factors, lifestyle, menopause, and aging. Secondary osteoporosis that is caused by a disease, such as hyperparathyroidism, can be improved by treating the underlying disease.

Hyperparathyroidism can be classified into either primary hyperparathyroidism, a disorder of the parathyroid itself, or secondary hyperparathyroidism, a pathological state secondary to other disorders, such as chronic kidney disease or vitamin D deficiency/depletion. In both types of hyperparathyroidism, excessively secreted parathyroid hormone promotes bone turnover and consequently decreases the BMD, resulting in an increased fracture risk. However, the therapeutic strategies employed for each type are entirely different. Primary hyperparathyroidism is treated mainly by parathyroidectomy, and there is no evidence regarding pharmacologic treatment. Secondary hyperparathyroidism improves with treatment of its underlying disease. Hyperparathyroidism secondary to CKD should be treated in accordance with the Japanese Evidence-based Practice Guideline for the Treatment of CKD.

In rheumatoid arthritis, bone resorption increases and BMD decreases because of several factors, including activation of inflammatory cytokines, immobility, and use of glucocorticoids. Consequently, the fracture risk increases. Infliximab, an anti-TNF agent used to treat rheumatoid arthritis, increases BMD in patients with osteoporosis secondary to rheumatoid arthritis. Among the useful therapeutic medications for osteoporosis, bisphosphonates reduce fracture risk.

Osteoporosis secondary to lifestyle-related diseases

In recent years, it was demonstrated that bone metabolism is influenced by some atherosclerosis-inducing disorders such as diabetes mellitus, dyslipidemia, hypertension, and chronic kidney disease. In particular, osteoporosis caused by diabetes mellitus or CKD is established as "osteoporosis secondary to

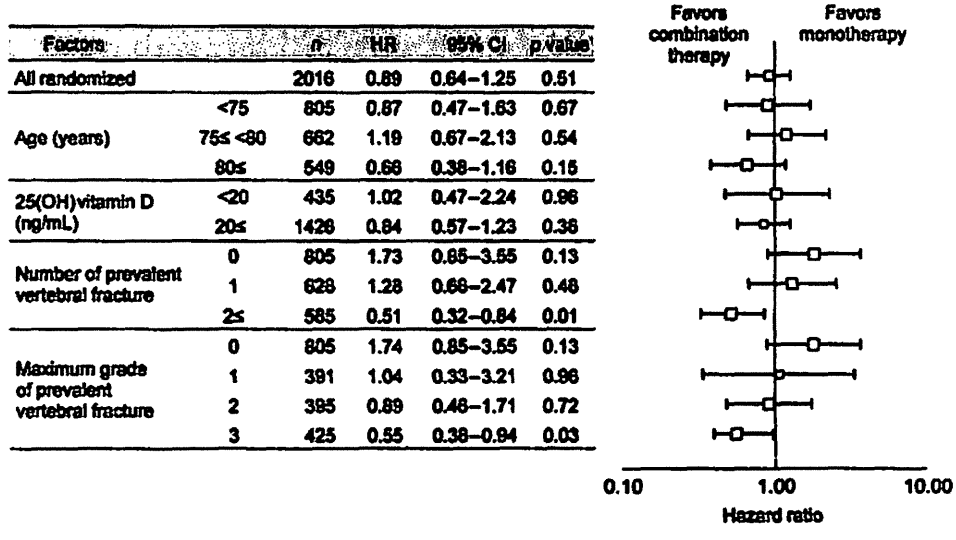

Fig. 14 Efficacy of combination therapy with alendronate and active vitamin D_3 on vertebral fracture. *HR* hazard ratio of incident vertebral fracture, *CI* confidence interval (Orimo [18] (Copyright© 2011 Informa Plc.))

lifestyle-related diseases", bringing it special attention within secondary osteoporosis. A vigorous assessment for osteoporosis is recommended in patients with these diseases.

Osteoporosis secondary to lifestyle-related diseases is mainly associated with deterioration in bone quality, whereas BMD is relatively well-preserved in most cases. Therefore, therapeutic intervention in patients with diabetes mellitus or CKD should be started as soon as "decreased bone mass" is identified, in accordance with the diagnostic criteria of osteoporosis.

The main cause of deterioration in bone quality in these patients is thought to be altered cross-links among the collagen molecules in bone tissue (nonphysiological collagen cross-links, i.e., advanced glycation endproducts) due to an increase in oxidative stress and acceleration of glycation.

While the therapeutic modality has not been established yet, the benefit of alendronate, risedronate, raloxifene, and parathyroid hormone derivatives has been reported in large clinical trials. Pentosidine is likely to be a marker for bone quality and is expected to be an index of the fracture risk.

Treatment-related osteoporosis

Glucocorticoid agents and sex hormone lowering therapy are important causes of treatment-related osteoporosis.

Systemically administrated glucocorticoid decreases bone mass and increases fracture risk, thus 50 % of patients under long-term treatment with glucocorticoids suffer from osteoporosis. In general, patients taking glucocorticoids at doses of 5 mg (prednisolone equivalent) or more per day for 3 months or more should be assessed for bone mass and the need for osteoporosis treatment. Moreover, it is recommended to start treatment at higher BMD values than those used in the criteria for treatment of primary osteoporosis. In Japan, a revision of the 2004 "Guidelines on the management and treatment of corticosteroid-induced osteoporosis" is being developed.

Even though guidelines currently recommend bisphosphonates for the treatment of glucocorticoid-induced osteoporosis, generally they are not recommended for women intending to become pregnant. Although teriparatide is expected to increase bone mass, it is indicated only for "osteoporosis with a high risk of fractures".

Endocrine therapy (sex hormone lowering therapy) for breast cancer and prostate cancer decreases BMD. Bisphosphonates can improve BMD in these patients, but there is no evidence yet about its ability to reduce fracture risk.

Conflicts of interest None.

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Association of *CYP19* Gene Polymorphism with Vertebral Fractures in Japanese Postmenopausal Women

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Abstract This study investigates aromatase gene polymorphism, which might influence bone strength in terms of mineral density and quality. We explored the relationship between *CYP19* polymorphisms and vertebral fractures in postmenopausal Japanese women. In addition, we compared estrogen and testosterone levels in Japanese postmenopausal women with and without fractures. Osteoporotic postmenopausal women showed higher incidences of vertebral fractures than osteopenic women or women with normal lumbar bone mineral density (L2-4 BMD). Estrogen concentrations in postmenopausal women were associated with BMD; however, no association was found between sex hormone levels and the presence of fractures. The C allele rs2470152 was significantly associated with increased risk of vertebral fractures ($P = 0.04$), whereas none of the *CYP19* polymorphisms showed differences in sex steroid levels between subjects with and without fractures. Allelic variants of aromatase genes appear to interact to influence the risk of vertebral fractures in postmenopausal Japanese women.

Keywords Aromatase gene polymorphisms · Vertebral fractures · Postmenopausal women

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Introduction

Osteoporosis is caused by multiple factors, including environmental factors (such as calcium intake), exercise, and estrogen levels. The main source of estrogen in postmenopausal women is the aromatization of androgenic precursors, a reaction catalyzed by the cytochrome P450-(CYP) aromatase enzyme, encoded by *CYP19* located on chromosome 15q21.1. It has recently been reported that estrogen levels are genetically determined by aromatase activity (Olson et al. 2007; Haiman et al. 2007; Sowers et al. 2006). In addition, allelic variants of the aromatase gene have been associated with bone mineral density (BMD) and bone fractures (Hong et al. 2007; Masi et al. 2001; Somner et al. 2004). A/G polymorphisms in the 3′ untranslated region (UTR) and the I.2 promoter (rs10046 and rs1062033; Rinancho et al. 2005) and an A/G polymorphism in the I.6 promoter rs4775936 (Enjuanes et al. 2006) of the aromatase gene have been studied in relation to osteoporosis and BMD, but the results remain controversial. In addition, an rs2470152 polymorphism in the aromatase gene has been shown to affect serum estrogen levels in Swedish men (Eriksson et al. 2009). Therefore, in order to analyze the association with the risk of vertebral fractures in postmenopausal women, we conducted a cross-sectional study of the interaction between *CYP19* gene polymorphisms and sex steroid hormone levels or risk of vertebral fractures in Japanese postmenopausal women. In this study, we focused on four markers (rs2470152, rs4775936, rs1062033, and rs10046) to clarify the association between polymorphisms in aromatase genes and vertebral fractures.

Materials and Methods

Study Subjects

Three hundred sets of genomic DNA and serum samples were provided from the collected samples of the Institute of Medical Sciences, Tokyo University, obtained for tailor-made medicine realization projects. These samples were collected from the various institutions that were members of these projects following the approval of the individual ethics committees. Ethical approval was obtained from the Ethics Committee of the Leading Project for Personalized Medicine in the Institute of Medical Science, University of Tokyo, and the Tokyo Metropolitan Geriatric Hospital. Another 300 DNA samples were collected from women for the purpose of analyzing the relationship between polymorphisms and the etiology of disease in the Japanese population. The samples were provided by the Leading Project for Personalized Medicine of the Ministry of Education, Culture, Sports, Science and Technology, Japan.

The samples were divided into three categories according to the *T* score of the measurement of lumbar spine BMD (L2-4 BMD) by dual energy X-ray absorptiometry (DXA) as defined by the World Health Organization: *T* scores of −1.0 and above were classified as normal BMD, scores of −2.5 to −1.0 were considered osteopenia, and scores below −2.5 were considered osteoporotic.

For assessment of vertebral fractures, anteroposterior and lateral X-ray examinations of the thoracic and lumbar spine were performed. Morphometrically,

a vertebral fracture was defined in terms of the ratio of the anterior height of vertebral body to the posterior height (below 0.75) or the ratio of the center height to the anterior or posterior height (below 0.8). In all cases, the vertebral fractures were evaluated by two groups of radiologists and geriatricians in each institute.

Sex Steroid Assay

The serum levels of testosterone (T) and estradiol (E_2) were measured by mass spectrophotometry (LC–MS/MS). Bioavailable testosterone and estrogen, which includes the free form and the albumin-binding form, were measured by LC–MS/MS (Arai et al. 2010). Serum samples were stored at −70°C until analyzed. For statistical analysis, the values were transformed into logarithmic form, since the values are exponential and the distributions of T and E_2 levels were skewed using the raw data.

Genotype Analysis

We examined four polymorphisms of *CYP19*: rs1062033, a G/C SNP located at around exon 1.2 (at position chromosome 15, 49335230); rs10046, a T/C SNP located in the 3′ UTR (at position chr.15, 49290276); rs4775936, a C/T SNP located in the vicinity of exon 1.6 (at position chr.15, 49323314); and rs2470152, a T/C SNP located in intron 1 (at position chr.15, 49382254). These SNPs were identified by searching the National Center for Biotechnology Information (NCBI) database because they are analyzable by the readily available TaqMan assays used for disease association studies (Applied Biosystems). Polymorphisms in genomic DNA were measured by the TaqMan assay. Age, body mass index, and years since menopause were examined in three SNP genotypes among four *CYP19* markers.

Statistical Analyses

Chi-square analysis was used to compare the numbers of osteoporosis, osteopenia, and normal patients by T scores of L2-4 BMD with and without fractures. Similarly, each parameter was compared among the three genotypes in four *CYP19* markers using ANOVA. The correlation between estradiol levels and L2-4 BMD was shown using Pearson's coefficients. The associations between aromatase gene polymorphisms and vertebral fracture risk were compared by Chi-square analysis using SPSS software.

Results

Bone Density Data

There were significantly more women with fractures than without among patients with osteoporosis ($T < -2.5$; $P < 0.05$), and there was no significant increase in fractures among normal patients or those with osteopenia. There were no differences

in the log estradiol (Log E_2) or log testosterone (Log T) values between women with fractures and those without fractures (Table 1).

Relationship Between L2-4 BMD and Estrogen level

Log E_2 levels in postmenopausal women were significantly associated with L2-4 BMD ($r = 0.21$, $p = 0.03$; Fig. 1), whereas log T levels showed no association (data not shown).

Genotype Analysis

When we examined the correlation between the four polymorphisms (rs2470152, rs1062033, rs4775963, and rs10046) and vertebral fractures in postmenopausal women, we found a significant correlation for rs2470152 ($P = 0.04$) but not for the

Table 1 Bone mineral density of postmenopausal women with and without fractures

T score[a] & sex steroids	Women without fractures (137)	Women with fractures (138)	P
$T < -2.5$	18	37	0.015
$-2.5 \leq T < 1.0$	12	13	NS
$-1.0 \leq T$	4	5	NS
Log E_2 (pg/ml)	0.335 ± 0.383	0.327 ± 0.330	NS
Log T (ng/dl)	2.033 ± 0.367	2.067 ± 0.247	NS

[a] Bone mineral density was measured in 89 of the 275 subjects

NS not significant

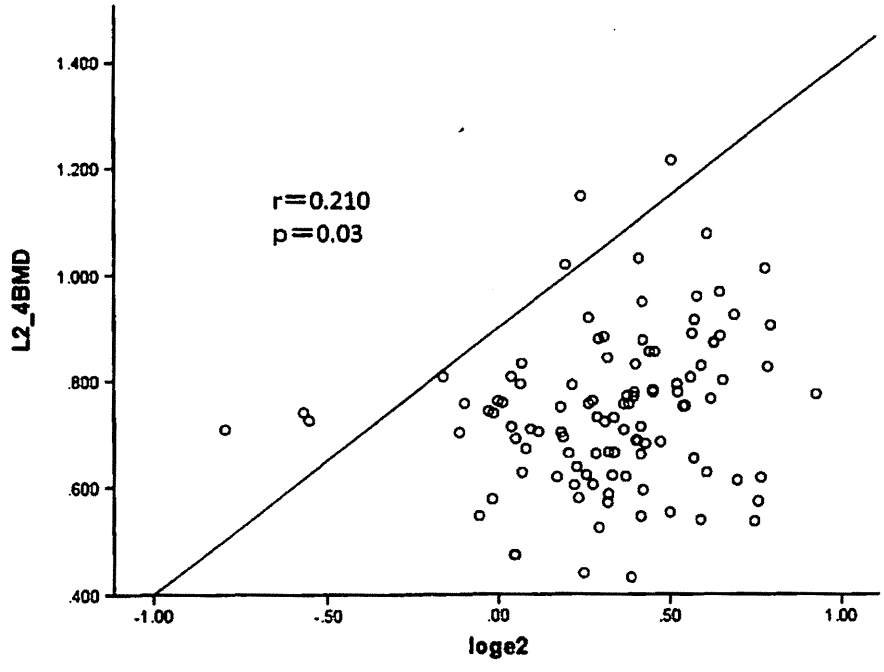

Fig. 1 Correlation between log E_2 and L2-4 BMD in postmenopausal women. Estrogen levels were significantly correlated with L2-4 BMD ($r = 0.21$, $p = 0.03$)

Table 2 Correlation of four *CYP19* SNPs with vertebral fractures

SNP	Genotype	Premenopause		*P*	Postmenopause		*P*
		Control ($n = 19$)	Case ($n = 6$)		Control ($n = 136$)	Case ($n = 138$)	
rs2470152	CC	9	1	0.408	44	47	0.040[a]
	TC	8	4		56	71	
	TT	2	1		36	20	
rs4775936	CC	5	1	0.712	48	59	0.416
	CT	9	4		68	59	
	TT	5	1		20	20	
rs1062033	CC	4	1	0.693	47	56	0.507
	CG	9	4		64	62	
	GG	6	1		25	20	
rs10046	TT	7	1	0.550	31	26	0.324
	TC	8	4		67	62	
	CC	4	1		38	50	

[a] Only rs2740152 polymorphisms of the aromatase gene showed a significant correlation with vertebral fractures ($P = 0.04$)

Table 3 Characteristics of postmenopausal Japanese women and three SNPs of rs2470152

Characteristic	Genotype			*P*
	CC	CT	TT	
Age (years)	72.8 ± 9.3	73.6 ± 8.3	74.3 ± 6.8	NS
Body mass index (kg/m^2)	22.4 ± 4.6	21.8 ± 4.5	21.1 ± 4.3	NS
Years since menopause	24.2 ± 9.5	24.3 ± 10.3	25.4 ± 11.6	NS
Log E_2 (pg/ml)	0.302 ± 0.319	0.330 ± 0.280	0.307 ± 0.357	NS
Log T (ng/dl)	2.001 ± 0.347	2.067 ± 0.269	2.050 ± 0.313	NS
L2-4BMD (110)	0.753 ± 0.135	0.739 ± 0.157	0.729 ± 0.118	NS
LT score (89)	−2.6 ± 1.2	−2.6 ± 1.3	−3.3 ± 0.8	NS

NS not significant

other three polymorphisms (Table 2). There were no differences in age, body mass index, or years since menopause among the three SNP types in the four *CYP19* markers (Table 3).

Discussion

We examined the relationship between aromatase-related genes and vertebral fractures by analyzing *CYP19* gene polymorphisms in Japanese women. Among four markers, no differences were found in serum T and E_2 concentrations in the Japanese postmenopausal women. It is possible that local E_2 concentrations are

more important in local tissues rather than serum levels. Bone cells are able to express aromatase and other enzymes required for estrogen synthesis locally (Janssen et al. 1999; Shouzu and Simpson 1998; Watanabe et al. 2004), and aromatase activity in cultured osteoblasts is quantitatively similar to that in adipose stromal cells (Shouzu and Simpson 1998). Thus, estrogen synthesized in bone cells might be important in postmenopausal bone metabolism.

Eriksson et al. (2009) found that genetic variants of rs2470152 in aromatase are associated with E_2 levels, showing that G alleles were correlated with higher serum E_2 levels and BMD in Swedish men than other alleles. Our results, however, showed that the C allele of rs2470152 is associated with vertebral fractures, a finding that suggests that ethnicity, race, and sex differences might influence the results of SNP studies in osteoporosis. The SNP rs2470152 is located in the region of the I.4 promoter (Bulun and Simpson 1994), and it is interesting that the G→A transition of rs2470152 is likely to alter a potential binding site for the binding protein of the transcription factor cAMP response element. The major reason for the discrepancy between our results and those of the Swedish study may be gender differences. The Swedish study focused only on male cohorts. We could not detect any disequilibrium between rs2470152 and the other three markers viewed in HapMap.

CYP19 SNPs (rs10046) were found to be associated with differences in E_2 levels in the European Prospective Investigation of Cancer-Norfolk (EPIC-Norfolk) cohort study (Dunning et al. 2004). SNP rs10046 explains 1.6% of the variance in the E_2:T ratio; however, this SNP is not associated with breast cancer risk (Dunning et al. 2004). The rs10046, a T/C SNP located in the 3′ UTR, 19 nucleotides downstream from the translation terminus, has been reported to be associated with increased levels of aromatase mRNA expression in tumors (Gruber et al. 2002). In our study, rs10046 was correlated with neither serum E_2 levels nor vertebral fractures. The *CYP19* genotypes demonstrated higher mRNA levels at the rs1062033 locus in postmenopausal osteoporosis. *CYP19* is regulated in a different manner and in different tissues by a hormonally controlled promoter or adipose stromal cell promoter (Mahendroo et al. 1993; Harada et al. 1993). Genetic polymorphisms of *CYP19* might be involved in other processes, such as mRNA stabilization, transcription enhancement, or the post-translational regulation of expression. Neither SNP 1062033 nor rs4775936 was significantly correlated with either serum E_2 levels or vertebral fractures.

We could not detect lower levels of bioavailable serum E_2 by LC–MS/MS in rs2470152; however, another group has shown differences in E_2 levels as measured by RIA according to *CYP19* genotype in a study that included both premenopausal and postmenopausal women (Somner et al. 2004). The discrepancy between the two studies seems to be due to the assay systems used. Bioavailable estrogen levels in postmenopausal women are more relevant than total estrogen levels, which include E_2 bound by sex hormone-binding globulin (SHBG), for bone metabolism. Despite the absence of differences in estrogen levels among the various genotypes, we found that vertebral fracture rates are associated with the *CYP19* genotype in postmenopausal Japanese women in this study. There is much evidence for the role of aromatase activity in bone homeostasis (Miyaura et al. 2001; Oz et al. 2000), and, as previously described, the pharmacological inhibition of aromatase is also associated

with a decrease in BMD and increased risk of fractures (Eastell and Hannon 2005). This indicates that aromatase in local tissues plays roles, both physiologically and pathologically, in bone metabolism.

In conclusion, we provide statistical evidence that the C allele in rs2470152 of the *CYP19* gene is associated with an increased risk of vertebral fractures in postmenopausal Japanese women. Further studies are necessary to detect functional SNPs that induce differences in bone metabolism. Furthermore, we need more participants to detect differences in E_2 levels based on the *CYP19* SNPs of aromatase genes.

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平成23年度骨粗鬆症財団研究助成ー①

Osteoporosis Japan

全国的データベースを用いた骨粗鬆症性骨折の予防と治療に関する研究

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1 研究の背景

高齢者における骨折は疼痛や変形によって日常生活活動度（ADL）を低下させ，生活の質（QOL）を悪化させる，いわゆる「寝たきり」の主要な原因のひとつである。さらに，高齢者の骨折は生命予後にも影響を与える重大な疾患である。高齢者の骨折で頻度の高いものとして，椎体骨折，前腕骨遠位端骨折，上腕近位部骨折，大腿骨近位部骨折などがあげられるが，これらを予防するためには，骨粗鬆症対策が欠かせない。骨粗鬆症は「骨強度の低下を特徴とし，骨折のリスクが増大しやすくなる骨格疾患」と定義され[1]，脆弱性骨折は本疾患の合併症として位置付けられる。

骨粗鬆症診療に関する全国的データの収集・解析を行うことにより，実際の診療現場での診断や治療の成果を解析することが欠かせない。このことを通じて，既存ガイドラインの客観的評価に役立つことも期待される。現在 1500～1600 億円ともいわれている骨粗鬆症治療薬に対する医療費の適正化に資する臨床研究は，社会的ニーズに即したものと考えられる。さらに骨折に関連する医療・介護費としては，薬剤費以外にも腰痛に対する外来・入院治療費，手術関連の医療費，リハビリテーションの費用，さらに長期療養にかかる費用も考えなければならず，これらの総額は 1 兆円にものぼることが推定されている。また，骨折や転倒予防に対する介入は全身の健康づくりにも寄与するものであることを考え合わせると，日常診療に基づくデータベータを用いた研究は骨折予防の総合的対策立案に重要な情報をもたらし，国民の保健・医療・福祉の全般的な向上にも結びつくことが期待される。

世界保健機構（WHO）が作成した fracture risk assessment tool（FRAX®）は，前向き 10 年間の骨折発生確率（主要骨粗鬆症性骨折と大腿骨近位部骨折について）を算定するツールである[2]。これは地域住民に関する疫学データをもとに作成されたものであり，その臨床的意義を検証する研究が求められている。

2 研究目的

本研究では日常の骨粗鬆症診療におけるデータを全国規模で収集し，骨粗鬆症性骨折の発症要因，骨粗鬆症治療薬の選択に及ぼす因子，骨粗鬆症の薬物治療による骨折予防効果などについて検討することを目的とする。

3 研究計画・方法

1）研究の概要

平成 18 年から 20 年の厚生科学研究長寿科学総合研究で構築された骨粗鬆症診療の全国的データベースを用いる[3]。データベース研究は前向きコホート研究であり，原発性骨粗鬆症または骨量減少の女性を対象とする。2 年おき経過情報

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表1　登録情報

- 登録番号
- 研究者名
- 登録データ入力年月日
- 生年月日
- 身長，体重
- 疾患名
- 脆弱性骨折
- 椎体部位・グレード
- 非椎体：大腿骨近位部，上腕近位，上腕遠位，骨盤，肋骨，その他
- 骨密度：測定日，部位，機種，測定値，単位，Tスコア，Zスコア
- マーカー：測定日，種別，キット名，測定値，単位，依頼測定機関
- 臨床検査：測定日，Ca，P，ALP，ALB，uc-OC，i-PTH，25OHVD
- 合併症：RA，糖尿病，高血圧，高脂血症，虚血性心疾患，脳血管障害，悪性腫瘍，認知症，パーキンソン病など神経疾患，不眠症，うつ病
- アンケート：喫煙，飲酒，納豆・牛乳の摂取，日常生活活動，骨折の家族歴，ステロイド服用，腰背部痛，月経，身長低下
- 介護度
- 骨粗鬆症に関する薬剤名

を取集し，骨折の発生等をイベントとして登録する。

研究分担者による症例登録に加えて日本骨粗鬆症学会の下部組織である骨粗鬆症至適療法研究会（A-TOP研究会）に参加している医療機関にも研究協力者として積極的に参加を呼びかける。

2）調査対象

登録の対象は医療機関を受診した女性の原発性骨粗鬆症もしくは骨量減少の患者であり，かつ研究に関する文書同意を取得した患者とする。

3）調査項目

調査担当医師は登録時の情報および2年後との定期観察時に情報をデータベースに登録するとともに，イベント（骨折）の発生時に，情報を追加登録する（**表1**）。

①登録時の収集情報

生年月日・体格：身長，体重・既存骨折の状況・骨密度・骨代謝マーカー・合併症の有無・患者アンケート（生活習慣，介護度など）・血液検査（Ca, P, ALP, ALB, Uc-OC, i-PTH, 25OHVDのうち，施設で測定が実施されているもの）・治療薬剤

②定期観察時の収集情報

来院継続・脱落の区分・死亡の有無・治療薬剤：骨粗鬆症治療の継続・切替状況，コンプライアンス，副作用・骨密度検査・骨代謝マーカー・介護度の評価：非該当，要支援1・2，要介護1・2・3・4・5度の区分

③イベント（新規脆弱性骨折）発生時

椎体骨折の場合：部位およびグレード

非椎体骨折の場合：部位および発生年月

④対象の追跡

2年おきの調査時に再来院のない対象患者は，電話にて調査担当医師により来院を依頼する。その上で来院のない患者は調査から除外する。

4）データベースへの登録方法

専用の登録システム（Satellite®：電助システムズ社）が組み込まれたUSBを用いて登録を行う。

5）倫理面の配慮

本研究は疫学研究に関する倫理指針およびヘルシンキ宣言に準拠して実施する。対象者には書面による説明と同意を得た。研究内容は国立長寿医療研究センターの倫理・利益相反委員会で審議され承認された。

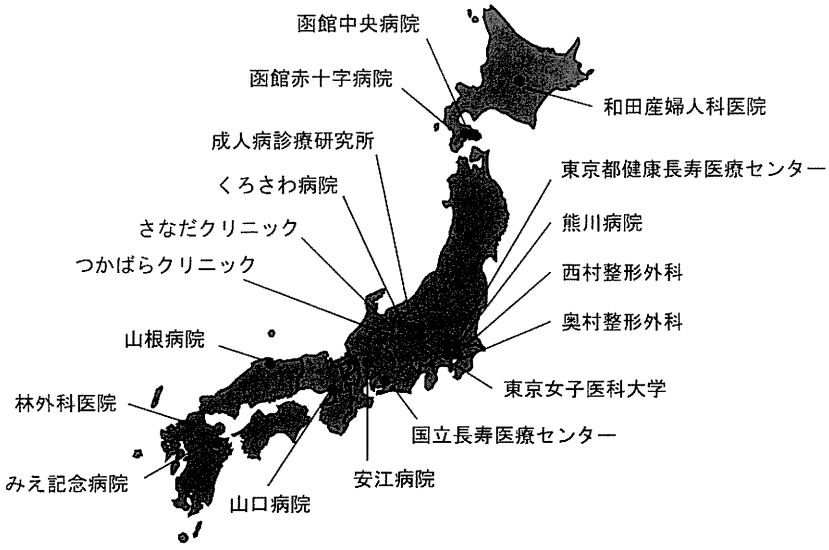

図1　登録地域と参加施設名

表2　背景情報：年齢，BMI，BMD

	Mean±SD	*n*
年齢（歳）	72.8±9.3	1482
身長（cm）	149.0±6.8	1472
体重（kg）	48.2±7.5	1470
BMI（kg/m²）	21.7±3.2	1470
BMD：T-score	−2.58±1.16	1079
BMD：Z-score	−0.45±1.19	1079

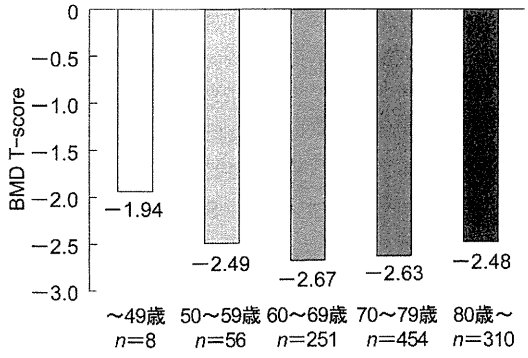

図2　背景情報：年齢とBMD（T-score）

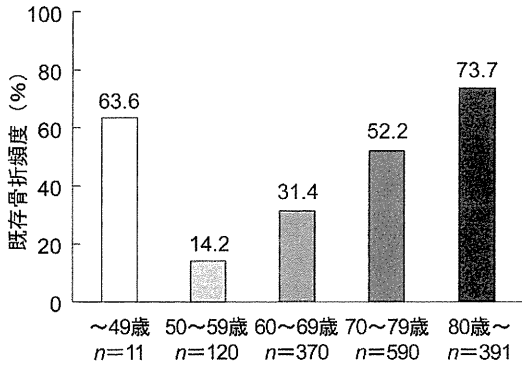

図3　背景情報：年齢と既存脆弱性骨折

4　研究結果

1）登録地域と例数

全国の18医療機関が研究に参加し総登録数は1482例であった（**図1**）。

2）年齢と骨密度の分布

登録症例の平均年齢は72.8歳であった。身長は149±6.8cm，体重は48.2±7.5kg，BMIは21.7±3.2であった（**表2**）。骨密度（BMD）の平均値はTスコアで−2.58±1.16，Zスコアで−0.45±1.19であり，Tスコアの年齢分布は**図2**に示すとおり，年齢依存性の差異は認めなかった。49歳以下の症例は8例ときわめて少なかった。

3）既存骨折の頻度と種類

脆弱性骨折をすでに有する者の割合は年齢依存性に増加する傾向が認められた（**図3**）。ただし49歳以下の集団では約64%に達しており，若年者における骨粗鬆症の薬物治療例は既存骨折

表3　背景情報：既存骨折

骨折区分	例数	頻度
脆弱性骨折あり	736/1482	49.7%
椎体	727/1482	49.1%
大腿骨近位部	8/1482	0.5%
上腕近位	6/1482	0.4%
上腕遠位	1/1482	0.1%
骨盤	1/1482	0.1%
その他	11/1482	0.7%

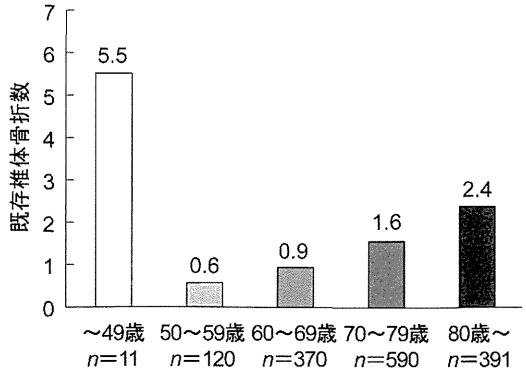

図4　背景情報：年齢と既存椎体骨折数

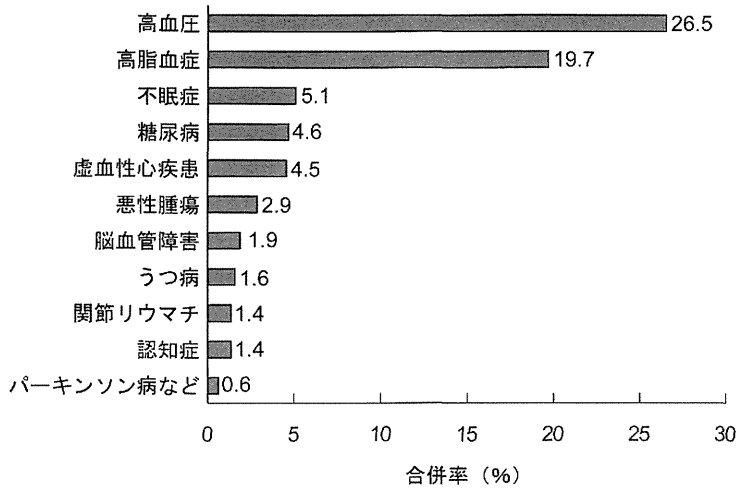

図5　背景情報：合併症

を有する割合が多く，骨折リスクが高いことがより注目されている結果であった。対象者全体での既存骨折の頻度は 49.7%であり，ほとんどが椎体骨折であった（**表3**）。椎体骨折の個数は年齢とともに増加する傾向がみられた（**図4**）。

4）併発症の頻度と既存骨折との関連

高血圧の併発率が 26.5%，高脂血症の併発率が 19.7%と，他の疾患に比べて高かった（**図5**）。併発症の有無で既存骨折の頻度を比較したところ，糖尿病と高血圧を有する場合と有さない場合との間で統計的な有意差を認めた（Student の *t* 検定）（**表4**）。認知症の有無についても統計的には有意差があったものの，認知症の症例数は極めて少なく，今回は臨床的意義を見出しかねるものと判断された。

5）骨粗鬆症治療薬の選択状況

対象者に対する薬物治療は，ビスホスホネート単独が最も多く，それにビスホスホネートと活性型ビタミン D の併用，SERM 単独，SERM と活性型ビタミン D の併用，活性型ビタミン D 単独，と続いた（**図6**）。それぞれの薬剤について既存骨折を有する者の割合を比較したところ，ビスホスホネート単独とビスホスホネートと活性型ビタミン D の併用群では既存骨折を有する者が上回っていた。一方，SERM においてはこの関係は逆転していた（**図7**）。

治療開始薬と FRAX®による 10 年間の主要骨粗鬆症性骨折発生確率との関連をみると，ビス

表4　背景情報：合併症有無別の脆弱性骨折頻度

種類	区分	脆弱性骨折			*p*
		無	有	%	
RA	無	737	724	49.5	0.490
	有	9	12	57.1	
糖尿病	無	722	692	48.9	0.011
	有	24	44	64.7	
高血圧	無	586	503	46.2	<0.001
	有	160	233	59.3	
高脂血症	無	598	592	49.8	0.895
	有	148	144	49.3	
虚血性心疾患	無	716	700	49.4	0.417
	有	30	36	54.6	
脳血管障害	無	737	717	49.3	0.052
	有	9	19	67.9	
認知症	無	742	720	49.3	0.006
	有	4	16	80.0	
うつ病	無	736	723	49.6	0.507
	有	19	13	56.5	

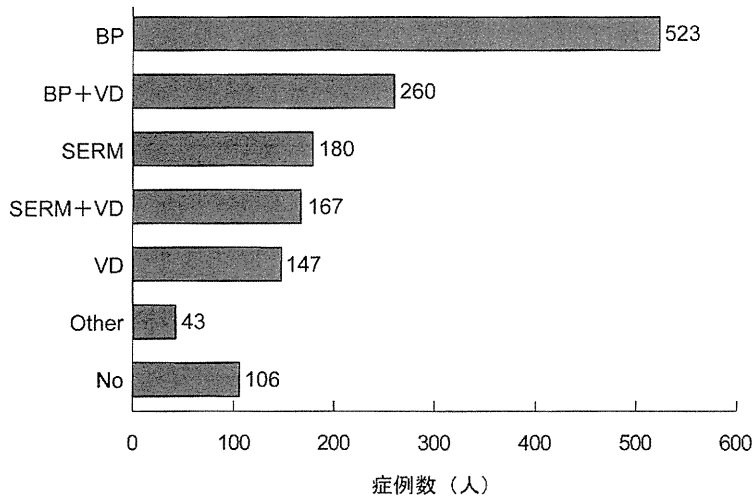

図6　薬物治療

ホスホネート単独，ビスホスホネートと活性型ビタミンDの併用，活性型ビタミンD単独の3群については，主要骨粗鬆症性骨折の確率，大腿骨近位部骨折の確率ともほぼ同等であった（**図8**）。

治療薬の選択と年齢との関連をみると，高齢者ほどビスホスホネート単独または併用群，活性型ビタミンD単独群が増加し，SERM単独または併用群が減少する傾向が観察された（**図9**）。

6）新規骨折の発生状況

2年間の経過を終え，現時点でデータが回収された1031例について新規骨折の発生状況を検討したところ，1031例中124例（12%）で新規骨折の発生が認められた（**表5**）。椎体骨折が多く

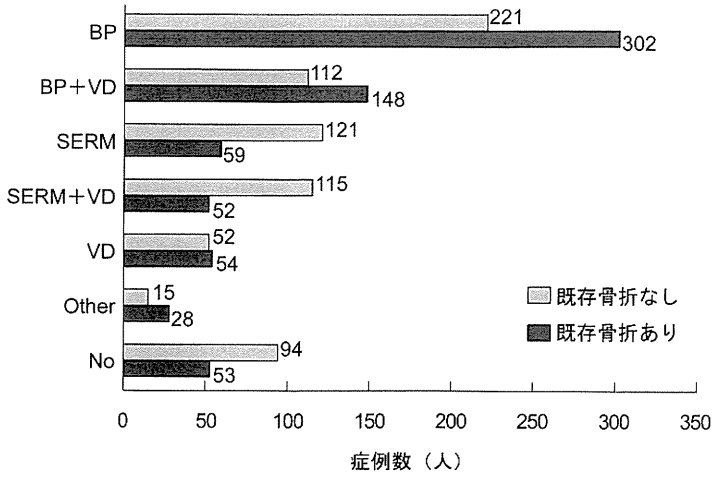

図7　既存骨折と薬物治療

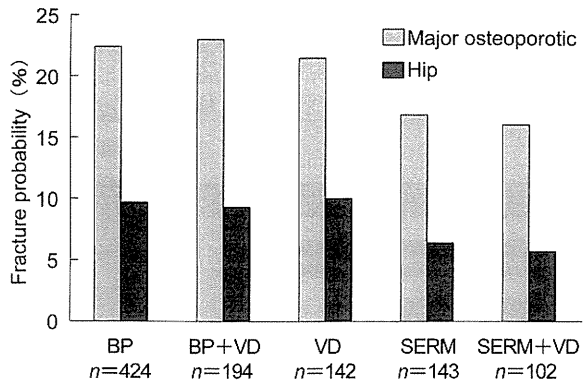

図8　治療開始薬とFRAX®

の部分を占め，四肢の骨折は3例のみだった。

新規脆弱性骨折の発生頻度は加齢とともに上昇した（**図10**）。一方，登録時の既存脆弱性骨折の有無は新規骨折の発生に大きな影響を及ぼしていることがうかがわれた（**図11**）。

7）新規骨折の発生頻度と治療薬との関連

今回の集計においては年齢や骨折危険因子などによる補正などを行っていないが，治療薬別の新規骨折発生頻度を比較した（データ未公表）。ビスホスホネートやSERMに対する活性型ビタミンDの併用効果が示唆された。

5　考　　察

今回の参加施設は日本骨粗鬆症学会のA-TOP研究会の参加施設でもあり，骨粗鬆症の診療に積極的に取り組まれている施設であると考えられる。研究デザインはこれらの施設における日常診療の結果を追跡するものであり，薬物の選択についてもそれぞれの担当医の判断に委ねられたものである。これらのことを踏まえると，このたび得られた結果は，わが国における骨粗鬆症診療に関する情報を十分に得ている担当医のプラクティスの現状を反映したものであると考えられる。このため，この結果をわが国の骨粗鬆症診療全体に外挿することには注意を払う必要がある。

ベースラインデータにおいては年齢依存性に既存脆弱性骨折の頻度や椎体骨折の数が上昇す

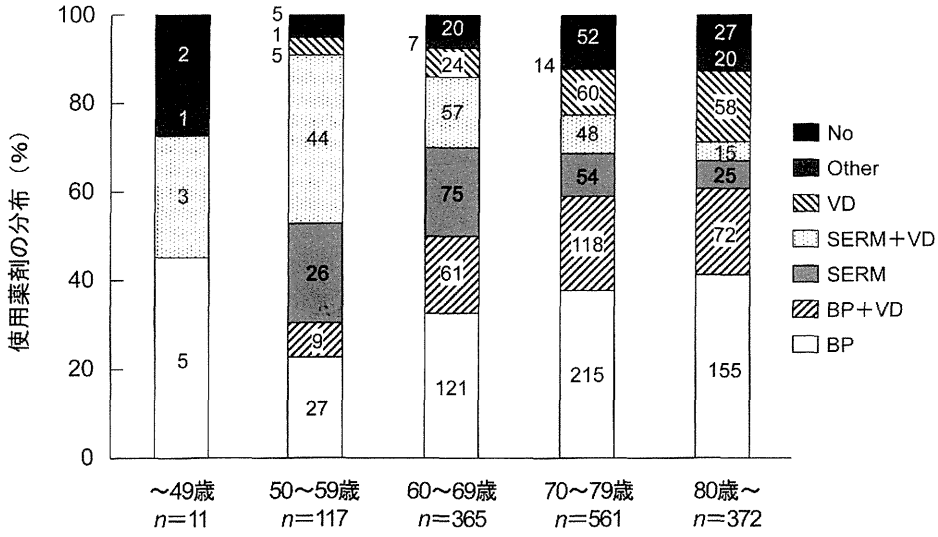

図9　年齢と薬物治療

表5　2年間の観察期間中の新規骨折の発生状況

脆弱性骨折あり	124/1031	12.0%
発生部位（既に収集されたもの）		
・椎体	92例	
・左大腿骨転子部	1例	
・左脛骨近位端	1例	
・脊骨	1例	
・大腿骨近位部	1例	
・椎体＋肋骨	1例	
・肋骨	1例	

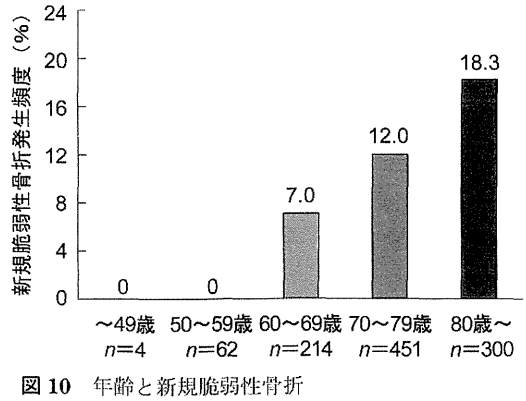

図10　年齢と新規脆弱性骨折

ることが認められ，対象者の集団が日本人骨粗鬆症集団を代表している面を有していることがうかがわれた。一方，49歳以下の集団は症例数が少なかったために他の年齢群とは直接的な比

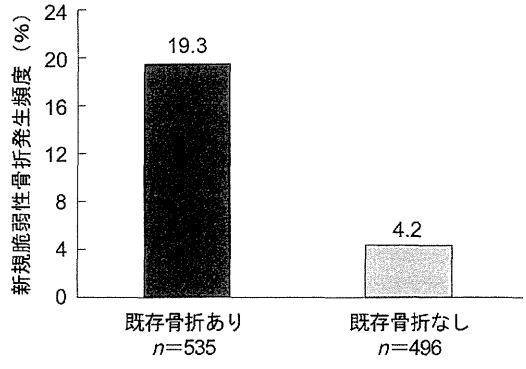

図11　既存骨折の有無と新規脆弱性骨折

較は困難ではあるものの，特殊な背景を備えている可能性が示唆された。

近年，生活習慣病による骨折リスクの上昇が注目されているが[4]，本研究においても糖尿病や高血圧の存在が骨粗鬆症性骨折と関連することが示唆され興味深い。

骨粗鬆症治療薬の選択においては，既存骨折の有無や骨折リスクの高さ，年齢などが考慮されていることがうかがわれた。骨折リスクの上昇において年齢は大きく寄与するものであり，薬剤選択における他の要因との関連をさらに検討すべきであろう。「骨粗鬆症の予防と治療ガイドライン2011年版」[5]では，骨粗鬆症の薬物治

療対象として，骨粗鬆症と診断された患者以外にもそれと同等かそれ以上の骨折リスクを有する患者が含められている。

2年間の観察期間中，12%で新規骨折が認められた。本研究の対象者はすべて薬物治療を行った者であることを前提にこの数値を考察する必要性がある。プラセボ群がないために，発生頻度の絶対値を議論することは困難であるが，ビスホスホネートに対する活性型ビタミン D_3 製剤の併用効果がうかがわれた。A-TOP 研究会の JOINT-02 研究では，椎体骨折を複数もつ例や椎体骨折による変形程度が強い例において併用療法の有用性が認められたが[6]，今回の調査ではこのような層別解析をしなくても併用療法の有用性が検出される可能性があり，さらなる解析が待たれる。また，SERM に対しても活性型ビタミン D_3 製剤を併用することの有用性がうかがわれた。これらのことは，本データベースに登録された患者集団の特性を反映していることも考えられる。

現在2年間の経過観察データの回収が最終段階にあり，最終的なデータセットについて詳細な検討を加えたうえでの報告を行う予定である。

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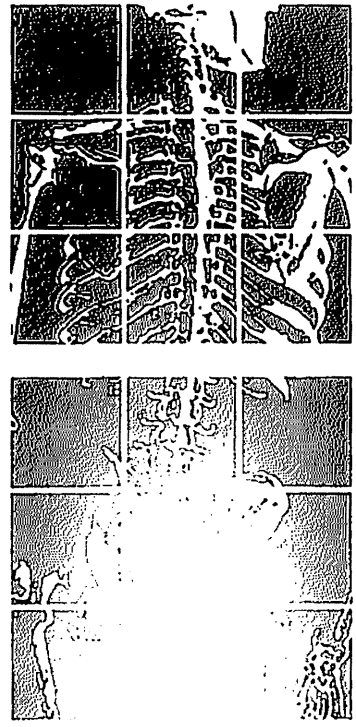
BASIC KNOWLEDGE



BASIC KNOWLEDGE

骨粗鬆症講座

Q&A

ガイドラインの改訂

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