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ORIGINAL ARTICLE

RISK FACTORS OF OSTEOPOROSIS ACCORDING TO THE NUMBER OF YEARS AFTER MENOPAUSE

Koshi Sumigawa[1, 2)], Ippei Takahashi[1)], Masashi Matsuzaka[1)], Kazuma Danjo[1)], Shuhei Koeda[1, 3)], Yuichi Hirakawa[2)], Terumi Kogawa[2)], Hidefumi Kamitani[3)], Takashi Umeda[1)] and Shigeyuki Nakaji[1)]

Abstract **Purpose:** To clarify how osteoporosis is influenced by the period after menopause. **Methods:** Our participants comprised 756 females. We used a questionnaire to ask participants about their lifestyle, number of deliveries, and age at which menopause occurred. We measured bone density, body mass index (BMI), body fat percentage (BFP), total body muscle index (TBMI), and lower limb muscle index (LLMI) during each of the following periods: before menopause, up to 15 years after menopause, and more than 16 years after menopause. **Results:** TBMI, BMI and BFP were significantly higher in premenopausal participants with higher bone density. Furthermore, higher bone density was observed in participants who had given birth fewer times had a and higher frequency of exercise. TBMI, LLMI, BMI and BFP were significantly higher in participants up to 15 years after menopause with higher bone density, and a trend wherein they were higher in participants who had progressed significantly fewer years after menopause was observed. TBMI, LLMI and BMI were significantly higher in participants more than 16 years after menopause with higher bone density. **Conclusion:** Risk factors for osteoporosis differed according to the number of years after menopause. Especially for postmenopausal women, it is important to maintain/increase lower limb muscle mass.

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Key words: bone density; years since menopause; lifestyle; muscle volume.

原 著

閉経後年数による骨粗鬆症要因の検討

澄川幸志[1, 2)] 高橋一平[1)] 松坂方士[1)] 檀上和真[1)]
小枝周平[1, 3)] 平川裕一[2)] 古川照美[2)] 上谷英史[3)]
梅田孝[1)] 中路重之[1)]

抄録 骨粗鬆症の予防には，骨密度の維持が重要であり，骨密度低下のリスク要因を知る必要がある．骨密度は，閉経や対象者の体格や筋肉量，さらには生活習慣の影響をうけるなど一つの因子で説明できるものでもない．そこで，本研究では一般女性を対象として，閉経後女性の骨密度の与える影響について多面的に検討した．対象は一般成人女性756名．対象者を閉経前，閉経後15年まで，閉経後16年以上に区分した．調査項目は，生活習慣，生殖歴，骨密度，身体測定である．その結果，閉経前は，全身筋肉指数，BMI(body mass index)，体脂肪率が高く，運動頻度が多く，分娩回数が少ない者ほど骨密度が高かった．閉経後15年までは，全身および下肢筋肉指数，BMI，体脂肪率が高く，閉経後年数が短い者，分娩回数が少ないものほど骨密度が高かった．閉経後16年以上は，全身および下肢筋肉指数，BMI が高い者ほど骨密度が高かった．以上のことより，閉経後女性の骨密度は閉経後年数により受けるリスクが異なることが示され，これらの因子を考慮した骨密度減少対策が求められると考えられた．

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キーワード：骨密度；閉経後年数；生活習慣；筋肉量.

[1)] Department of Social Medicine, Hirosaki University Graduate School of Medicine
[2)] Department of Health Promotion, Division of Health Sciences, Hirosaki University Graduate School of Health Sciences
[3)] Department of Development and Aging, Division of Health Sciences, Hirosaki University Graduate School of Health Sciences
Correspondence: K. Sumigawa
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[1)] 弘前大学大学院医学研究科社会医学講座
[2)] 弘前大学大学院保健学研究科健康支援科学領域健康増進科学分野
[3)] 弘前大学大学院保健学研究科健康支援科学領域老年科学分野
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Introduction

Osteoporosis is a global problem in rapidly aging modern societies[1]. In Japan, osteoporotic fractures of the elderly are a major problem that can cause patients to be bedridden. Moreover, it is clear that bone fractures shorten life expectancy and cause drastic decreases in the quality of life (QOL) [2]. It is thus extremely important to create strategies to combat osteoporosis. Moreover, this disease is 3 times more prevalent in women than in men[3], and the rate of decreased bone density (BD) for patients over 60 years of age is higher in women[4]. Thus, it is vital that strategies for the prevention of osteoporosis are implemented more promptly in women than in men.

To prevent osteoporosis, it is important to understand the risk factors for decreased BD [5]. Many previous studies have identified menopause as an important risk factor for osteoporosis in women. When women reach menopause, the secretory capacity of estrogen decreases, thereby accelerating bone resorption[6, 7]. Okano et al. showed that the rate of annual change in the BD of women who were menopausal for 1–3, 4–6, 10–12, and more than 13 years was -3.1%, -1.2%, -1.0%, and -2.3%, respectively[8]. In addition, the incidence of osteoporosis was found to rise suddenly after the onset of menopause[6].

In recent years, studies have shown that BD differs according to the number of postmenopausal years. Previous studies have shown that the largest reductions in BD occur 5 years after menopause, after which declines in BD become progressively smaller[9, 10]. On the other hand, another study indicates that menopause has almost no effect on BD 15 or more years after its onset[11]. Thus, the relationship between menopause and BD is still a controversial issue.

Menopause is also known to influence other risk factors for osteoporosis. For example, with regard to physique and body composition, menopause increases body weight and body fat percentage (BFP) and reduces muscle mass[12, 13]. With respect to muscle mass in particular, lower limb muscle mass markedly decreases[14, 15]. However, no studies have yet examined the influence of menopause, body composition, and lifestyle on BD at the same time. Therefore, we examined their impact in women before menopause, 15 or fewer years after menopause, and 16 or more years after menopause.

Methods

(1) Participation rate

Between 2006 and 2010, the average population of females over 20 years of age in the subject area (Iwaki district in Hirosaki City) was 4,768. Approximately 1 month before the check-up day, we posted a set of documents, including a self-administered questionnaire, an explanatory text, and a written consent form, for all female residents over 20 years of age. One thousand one hundred sixty-four women agreed to participate in the health check-ups from 2006 to 2010. Thus, the participation rate of the subject area was 24.4%. The health check-ups were carried out for approximately 2 weeks in June of each year.

Targeting the female population in the Iwaki area, this study aimed to comprehensively evaluate the current health statuses and problems of residents from a medical perspective. It has 2 principal objectives: (1) to contribute to the maintenance and promotion of health and the improvement of the daily QOL of Iwaki's female residents and (2) to comprehensively research strategies for the prevention of osteoporosis. After excluding women with a history of diabetes and gynecological and orthopedic diseases (fractures, osteoporosis, rheumatoid arthritis), and those receiving steroid or hormone therapy, 756 women (64.9%) were included in this study. Thus, the final participation rate was 15.9%.

(2) Measurement items and methods

We measured the height, weight, body composition, and BD of participants and conducted medical interviews with them.

Body weight was determined with a Tanita Model TBF 310 GS Weight Scale (Tanita Corp. Tokyo, Japan). During weighing, subjects wore lightweight clothing and no shoes. Height, without shoes, was determined using a wall-mounted stadiometer. The subject's BMI was computed from the height and weight measurements (kg/m^2).

We used the Tanita MC-190 body composition analyzer (Tanita Corp. Tokyo, Japan) to measure BFP and muscle mass with bioelectrical impedance analysis (BIA). Participants were asked to stand bare feet on the analyzer and grip its metallic handles. Small electrical currents were sent through the handles to various areas of the body, and the electrical resistance was measured to determine the fat percentage of various tissues. As this device uses multiple frequencies (5 kHz, 50 kHz, 250 kHz, and 500 kHz) for its analysis, it measures body composition with higher precision than other traditional devices using BIA. This measurement method has been used in numerous studies that have targeted a range of participants, from children to adults[16-20]. A strong correlation has been reported between the impedance value and body composition value, measured with dual-energy X-ray absorptiometry (DXA) [21]. Furthermore, the muscle mass appraised with this device includes skeletal muscle and smooth muscle body water content. The measured value is the tissue mass of body weight minus any fat and bone mineral content. In addition to total body muscle mass, this device can separately measure the muscle mass of areas such as the upper limbs, lower limbs, and trunk. Because height influences total body muscle mass, we used total body muscle mass divided by height squared as the total body muscle index (TBMI). Likewise, we employed lower limb muscle mass divided by height squared as the lower limb muscle index (LLMI). Previous studies have utilized these muscle indices in considering the influence of height on muscle mass[22, 23].

BD was determined by measuring the osteo sono-assessment index (OSI) of the calcaneus with quantitative ultrasound (QUS). We exposed the right calcaneus to ultrasonic waves by using a calcaneus osteo sono-assessment device (ALOKA, AOS-100NW), which measures the speed of sound (SOS) and transmission index (TI) and exploits them to calculate the OSI. The formula OSI = TI $\times$ SOS^2 is used, since it reflects the characteristics of SOS and TI; we employed the OSI as an index for BD. The QUS method for measuring bone mass in the calcaneus is a suitable method for screening for osteoporosis, given its safety and simplicity.

For our medical interviews, we used a self-administered questionnaire that gathered information on age, reproductive history, and lifestyle. The reproductive history item included questions regarding the age of onset of menopause and the number of deliveries. The lifestyle item comprised questions on the number of cigarettes smoked per day, the amount of alcohol consumed per day, and the number of times exercise was performed per week.

(3) Statistics and analysis

We classified participants into 3 groups: premenopausal women, women with 15 or fewer postmenopausal years, and women with 16 postmenopausal years. We then divided each group into 3, based on OSI values, which resulted in low, medium, and high percentile groups. The TBMI, LLMI, BMI, and BFP of these 3 OSI groups were compared with an analysis of covariance (ANCOVA) and the Bonferroni method, after adjusting for age, number of deliveries, and lifestyle categories (smoking habits, alcohol intake, and exercise

Table 1 Characteristics of subjects

	Before menopause (n=275)	Up to 15 years after menopause (n=290)	16 years or more after menopause (n=191)
Age (years)	39.3 ± 8.5	58.0 ± 5.3 **	71.4 ± 4.7 **††
Height (cm)	158.3 ± 5.1	153.2 ± 4.7 **	148.5 ± 5.6 **††
Weight (kg)	55.1 ± 8.7	54.3 ± 7.9	51.7 ± 7.5 **††
BMI (kg/m^2)	22.1 ± 3.5	23.2 ± 3.2 **	23.4 ± 3.0 **
Body fat percentage (%)	28.1 ± 6.9	30.1 ± 6.8 **	31.5 ± 6.5 **
Total body muscle index (kg/m^2)	14.8 ± 1.1	15.1 ± 0.8 **	15.0 ± 1.0
Lower limb muscle index (kg/m^2)	5.3 ± 0.5	5.1 ± 0.4 **	4.8 ± 0.5 **††
Number of cigarettes smoked (cigarettes/day)	3.1 ± 6.6	1.1 ± 3.7 **	0.3 ± 1.9 **
Alcohol intake (g/day)	1.9 ± 2.9	1.0 ± 3.1 **	0.3 ± 1.1 **††
Exercise frequency (times/week)	0.3 ± 1.1	0.8 ± 1.7 **	0.9 ± 1.9 **
Number of deliveries (number)	1.7 ± 1.1	2.3 ± 0.8 **	2.5 ± 1.0 **
OSI ($\times 10^6$)	2.8 ± 0.3	2.5 ± 0.3 **	2.3 ± 0.3 **††

Mean ± S.D. Multiple comparison between the groups was conducted using the Bonferroni method.
*: p<0.05, **: p<0.01*; Significant differences from before menopause
†: p<0.05, ††: p<0.01*;††: Significant differences from until 15 years after menopause

frequency). At the same time, the number of deliveries and lifestyle categories were also compared with an analysis of covariance (ANCOVA) and the Bonferroni method, after adjusting for age, BMI, and other lifestyle categories. We used SPSS 17.0 for statistical analysis. In this study, $p < 0.05$ indicated a significant difference, and $p < 0.1$ indicated the existence of a trend.

(4) Ethical considerations

We advised the participants of the purpose of the study verbally and through documentation; in addition, we informed them that they could discontinue their involvement at any time and that their anonymity would be protected. They were provided with an explanation of the methods used for data management. Written consent for participation in the study was then obtained from each participant. The Iwaki Health Promotion Project was conducted with the approval of the ethics committee of the Hirosaki University Graduate School of Medicine.

Results

Characteristics of participants

Table 1 shows the characteristics of the participants. The BMI, BFP, TBMI, LLMI, exercise frequency, and the number of deliveries were higher and cigarette and alcohol consumption and OSI lower in those with 15 or fewer postmenopausal years than in the premenopausal group. Women with 16 or more postmenopausal years had a higher BMI, BFP, LLMI, exercise frequency, and number of deliveries, smoked fewer cigarettes per day, and had a lower daily alcohol intake and OSI than did premenopausal women. Compared to women with 15 or fewer postmenopausal years, the LLMI, alcohol intake, and OSI were lower in women with 16 or more postmenopausal years.

Relationship between BD and body composition, reproductive history, and lifestyle habits of premenopausal and postmenopausal women

(1) Premenopausal women (Table 2)

The TBMI, BMI, BFP, and exercise frequency were significantly higher in participants with higher BD ($p = 0.020$, $p = 0.002$, $p = 0.002$, $p =$

Table 2 Relationship between BD and the body composition, reproductive history, and lifestyle habits of premenopausal women

	OSI ($\times 10^6$)			
	Low BD group (n=92)	Medium BD group (n=92)	High BD group (n=91)	P value
Total body muscle index (kg/m^2)[a)]	14.5 ± 0.1	14.9 ± 0.1	15.0 ± 0.1 *	0.020
Lower limb muscle index (kg/m^2)[a)]	5.2 ± 0.1	5.3 ± 0.1	5.4 ± 0.1	0.090
BMI (kg/m^2)[a)]	21.1 ± 0.4	22.4 ± 0.4 *	22.8 ± 0.4 **	0.002
Body fat percentage (%)[a)]	26.1 ± 0.7	28.9 ± 0.7 *	29.5 ± 0.7 **	0.002
Number of deliveries (number)[b)]	1.7 ± 0.1	1.9 ± 0.1	1.5 ± 0.1	0.057
Number of cigarettes smoked (cigarettes/day)[b)]	3.6 ± 0.7	2.7 ± 0.7	3.1 ± 0.7	0.630
Alcohol intake (g/day)[b)]	1.4 ± 0.3	2.1 ± 0.3	2.0 ± 0.3	0.250
Exercise frequency (times/week)[b)]	0.1 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.056

Mean ± standard error
a) A multiple comparison with the Bonferroni method was conducted after adjusting for total body muscle index, lower limb muscle index, BMI, and body fat percentage with age, number of deliveries, number of cigarettes smoked, alcohol intake, and exercise frequency using analysis of covariance.
b) A multiple comparison with the Bonferroni method was conducted after adjusting for number of deliveries, number of cigarettes smoked, alcohol intake, and exercise frequency with age and BMI; and lifestyle habits were not included as items under investigation using analysis of covariance.
Compared with the low group: (*:$p<0.05$, **:$p<0.01$).
Low BD group: those below the 34th percentile, Medium BD group: those below the 67th percentile, High BD group: those above the 67th percentile.
OSI: Osteo sono-assessment index
BD: Bone density

Table 3 Relationship between BD and the body composition, reproductive history, and lifestyle habits of women up to 15 years after menopause

	OSI ($\times 10^6$)			
	Low BD group (n=97)	Medium BD group (n=97)	High BD group (n=96)	P value
Total body muscle index (kg/m^2)[a)]	14.9 ± 0.1	15.2 ± 0.1 *	15.3 ± 0.1 **	0.002
Lower limb muscle index (kg/m^2)[a)]	5.0 ± 0.0	5.1 ± 0.0	5.2 ± 0.0 *	0.015
BMI (kg/m^2)[a)]	22.0 ± 0.3	23.5 ± 0.3 **	23.9 ± 0.3 **	0.000
Body fat percentage (%)[a)]	28.0 ± 0.7	30.6 ± 0.7 *	31.8 ± 0.7 **	0.001
Years after menopause (years)[b)]	7.9 ± 0.3	7.4 ± 0.3	6.4 ± 0.3 **†	0.002
Number of deliveries (number)[b)]	2.4 ± 0.1	2.4 ± 0.1	2.2 ± 0.1	0.097
Number of cigarettes smoked (cigarettes/day)[b)]	1.6 ± 0.4	0.9 ± 0.4	0.8 ± 0.4	0.412
Alcohol intake (g/day)[b)]	1.7 ± 0.3	0.7 ± 0.3	0.8 ± 0.3	0.110
Exercise frequency (times/week)[b)]	0.7 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.747

Mean ± standard error
a) A multiple comparison with the Bonferroni method was conducted after adjusting for total body muscle index, lower limb muscle index, BMI, and body fat percentage with age, years after menopause, number of deliveries, number of cigarettes smoked, alcohol intake, and exercise frequency using analysis of covariance.
b) A multiple comparison with the Bonferroni method was conducted after adjusting for years after menopause, number of deliveries, number of cigarettes smoked, alcohol intake, and exercise frequency with age and BMI; reproductive history and lifestyle habits were not included as items under investigation using analysis of covariance.
When compared with the low group: (*:$p<0.05$, **:$p<0.01$,). When compared with the medium group: (†:$p<0.05$).
Low BD group: those below the 34th percentile, Medium BD group: those below the 67th percentile, High BD group: those above the 67th percentile.
OSI: Osteo sono-assessment index
BD: Bone density

0.056, respectively), and the number of deliveries was lower in participants with higher BD ($p = 0.057$).

(2) Women with 15 or fewer postmenopausal years (Table 3)

The TBMI, LLMI, BMI, and BFP were significantly higher in participants with higher BD ($p = 0.002$, $p = 0.015$, $p = 0.000$, $p = 0.001$,

Table 4 Relationship between BD and the body composition, reproductive history, and lifestyle habits of women 16 years or more after menopause

	OSI (×10^6)			
	Low BD group (n=64)	Medium BD group (n=64)	High BD group (n=63)	P value
Total body muscle index (kg/m^2)[a)]	14.6 ± 0.1	15.1 ± 0.1 *	15.2 ± 0.1 **	0.005
Lower limb muscle index (kg/m^2)[a)]	4.6 ± 0.1	4.8 ± 0.1 *	4.9 ± 0.1 **	0.010
BMI (kg/m^2)[a)]	22.3 ± 0.4	23.6 ± 0.4	24.2 ± 0.4 **	0.003
Body fat percentage (%)[a)]	30.2 ± 0.8	31.4 ± 0.8	33.0 ± 0.8	0.073
Years after menopause (years)[b)]	22.9 ± 0.5	22.4 ± 0.5	22.4 ± 0.5	0.716
Number of deliveries (number)[b)]	2.5 ± 0.1	2.4 ± 0.1	2.5 ± 0.1	0.909
Number of cigarettes smoked (cigarettes/day)[b)]	0.6 ± 0.3	0.2 ± 0.2	0.1 ± 0.3	0.383
Alcohol intake (g/day)[b)]	0.3 ± 0.1	0.3 ± 0.1	0.2 ± 0.1	0.805
Exercise frequency (times/week)[b)]	0.7 ± 0.2	0.9 ± 0.2	1.1 ± 0.2	0.493

Mean ± standard error
a) A multiple comparison with the Bonferroni method was conducted after adjusting for total body muscle index, lower limb muscle index, BMI, and body fat percentage with age, years after menopause, number of deliveries, number of cigarettes smoked, alcohol intake, and exercise frequency using analysis of covariance.
b) A multiple comparison with the Bonferroni method was conducted after adjusting for years after menopause, number of deliveries, number of cigarettes smoked, alcohol intake, and exercise frequency with age and BMI; reproductive history and lifestyle habits were not included as items under investigation using analysis of covariance.
P value used for comparison with low BD group: (*:p<0.05, **:p<0.01,)
Low BD group: those below the 34th percentile. Medium BD group: those below the 67th percentile. High BD group: those above the 67th percentile.
OSI: Osteo sono-assessment index
BD: Bone density

respectively), and the number of deliveries and years after menopause were lower in participants with higher BD ($p = 0.002$, $p = 0.097$, respectively).

(3) Women with 16 or more postmenopausal years (Table 4)

The TBMI, LLMI, and BMI were significantly higher in participants with higher BD ($p = 0.005$, 0.010, 0.003, respectively).

Discussion

Risk factors for osteoporosis can differ depending on the number of years after menopause. However, no previous studies have focused on the analysis of their relationship. Our results reveal that the BMI, BFP, and TBMI were higher in postmenopausal than in premenopausal women. Furthermore, the LLMI was lower in women with 16 or more postmenopausal years than in those with 15 or fewer postmenopausal years. Previous studies have reported that muscle mass decreases and body fat volume increases after the onset of menopause[24, 25]; the decreases in lower limb muscle mass are said to be particularly notable[14, 15]. The reduced estrogen levels that accompany menopause, which undermine muscle maintenance and growth, appear to be the mechanism that causes muscle mass to decrease [26, 27].

Premenopausal women with higher BD had significantly higher TBMI, BMI, and BFP, and tended to exercise more frequently and have lower numbers of deliveries. Increased TBMI and BMI cause a greater load to be placed on bones and encourage increases in BD[28, 29]. Our results support those of previous studies. Meanwhile, participants with high BD also exhibited high BFP. Body fat is said to be correlated with BMI[30], and our study also showed that participants with high BMI had a high BFP ($r = 0.847$, $p < 0.01$). However, an increased BFP is a known risk factor for circulatory diseases, such as hyperlipidemia and arteriosclerosis, as well as other disorders[31]. Previous inquiries have indicated that in premenopausal women, lean body mass (muscle mass), rather than the amount of body fat, is crucial in the prevention of osteoporosis[32]. Our results support these findings. Moreover, we found that participants with higher BD engaged in exercise more frequently; it appears that these higher densities were produced by high osteoblast activity prior to menopause; thus, stimulation through exercise led to increased BD[33]. The number of deliveries for premenopausal women was also low in participants with higher BD. Previous studies have reported lower BD in women with many deliveries[34]. Lifestyle changes after childbirth decreased calcium in the bodies of mothers because of breast-feeding[35]; in this regard, the decreased calcium absorption caused by lower levels of serum estradiol has been suggested as an underlying mechanism[36, 37]. Therefore, it is extremely important for women to exercise more and increase their muscle mass before menopause. In particular, exercise frequency decreases and diet worsens in postpartum women, making it easier for their fat mass to increase[38, 39]. Therefore, increasing the awareness of these risk factors for osteoporosis and offering lifestyle advice to women from a young, prior to child-bearing age is essential not just to prevent osteoporosis but also to maintain overall health.

Women with 15 or fewer postmenopausal years with higher bone densities had significantly higher TBMI, LLMI, BMI, and BFP and showed a trend to exercise more frequently and have lower number of deliveries. Menopause is known to cause estrogen levels to drop, leading to decreased calcium absorption and increased bone resorption through osteoclasts, which in turn results in decreased BD[40, 41]. On the other hand, the participants with 15 or fewer postmenopausal years and higher bone densities had significantly higher BMI, BFP, and TBMI. This finding suggests that muscle mass is important in this group as well as in premenopausal women. In contrast to premenopausal women, women with 15 or fewer postmenopausal years with higher BD had higher LLMI. In postmenopausal women leads to decreased lower limb muscular strength, making it easier for them to slip and fall[42]. Strength training for this part of the body during this period may thus prevent falls as well as osteoporosis. In contrast, we found no relationship between BD and exercise frequency in postmenopausal women. Earlier studies have indicated that resistance training leads to greater increases in BD than does aerobic exercise and that the type of exercise performed is more important than the frequency of exercise[43].

Women 16 years or more after menopause with higher BD had a significantly higher TBMI, LLMI, and BMI as did women with 15 or fewer postmenopausal years. In addition, in contrast to premenopausal women and women with 15 or fewer postmenopausal years, the BFP had no significant effect on the BD of women with 16 or more postmenopausal years. This finding suggests that stimulation by muscular contraction, which augments muscle mass (and particularly lower limb muscle mass), appears to be more effective in increasing BD than fat mass[44]. We found a relationship between BD and the number of years after menopause and the number of deliveries in the group of women with 15 or fewer postmenopausal years, but no such relationship was identified in women with 16 or more postmenopausal years. Therefore, menopause and reproductive history may have a small affect on the BD in women more than 16 years after menopause.

However, the number of cigarettes smoked and the amount of alcohol consumed had no significant effect on BD in any of the groups. Previous studies have reported that more than 20 g of alcohol and more than 20 cigarettes per day are associated with reduced BD[45, 46]. Even in women in the premenopausal group, who smoked the greatest number of cigarettes and had the highest alcohol intake, the mean number of cigarettes smoked per day was 3.1 and the mean alcohol intake per day was 1.9 g. As such, the participants in our study appear to be a population with a low consumption of tobacco and alcohol; thus, these 2 substances were not significant risk factors for these participants.

Methodological limitations of this study are as follows: (1) The participants live in a rural area and are likely to have different dietary habits and lifestyles than urban women. Thus, they do not necessarily represent the whole female population of Japan. (2) This was not a population-based study. Thus, potential collection bias cannot be excluded. (3) We did not use any standard instruments for data collection.

Conclusion

Risk factors for osteoporosis differ according to the number of postmenopausal years. Throughout the lives of women, exercising is an important strategy for the prevention of osteoporosis, since it maintains and increases the total body muscle mass. Such maintenance and growth is especially crucial for postmenopausal women.

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