



10-Year Fracture Risk in Postmenopausal Women with Osteopenia and Osteoporosis in South Korea

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Background: In South Korea, women aged 66 years are eligible for complimentary bone mineral density (BMD) screening via the National Screening Program for Transitional Ages. We aimed to evaluate the 10-year fracture risk in women receiving BMD screening between January 2008 and December 2015.

Methods: BMD was classified as normal (T-score ≥ -1.0 standard deviation [SD]), osteopenia (T-score < -1.0 SD and > -2.5 SD), and osteoporosis (T score ≤ -2.5 SD) from dual-energy X-ray absorptiometry. Follow-up continued from the screening date until a diagnosis for clinical fragility fracture (including sites of the vertebrae, hip, pelvis, clavicle, humerus, forearm, wrist, lower leg, and ankle), censored at the earliest date of trauma, death, or December 2017; fracture was ascertained using diagnostic codes from the National Health Insurance Service database. A multivariable Cox proportional hazard model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of fracture in women with osteopenia or osteoporosis relative to women with normal BMD.

Results: Among the 271,197 women screened, 44.0% had osteopenia and 35.2% had osteoporosis. The 10 year cumulative incidence of fragility fractures was 31.1%, 37.5%, and 44.3% in women with normal BMD, osteopenia, and osteoporosis, respectively. Fracture risk was higher in women with osteopenia (HR, 1.31; 95% CI, 1.28 to 1.34) and osteoporosis (HR, 1.68; 95% CI, 1.64 to 1.72) than in women with normal BMD.

Conclusion: Women with osteopenia and women with osteoporosis, identified by the national BMD screening program, demonstrated a substantially elevated risk of fracture.

Keywords: Bone density; Bone diseases, metabolic; Fractures, bone; Osteoporosis; Postmenopause

INTRODUCTION

Osteoporosis is a metabolic bone disease characterized by loss

of bone mass and deteriorated bone microstructure, with a consequent increase in bone fragility and long-term fracture risk [1]. Impaired bone turnover cycles due to estrogen deficiency are

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associated with low bone mineral density (BMD) in postmenopausal women [2], resulting in an increased risk of fracture at sites such as the vertebrae and hip [3-5]. Osteopenia has traditionally been considered a precursor of future osteoporosis rather than an abnormal bone state with inherent fracture risk. However, the incidence of fragility fractures in osteopenia is substantial; 82% of postmenopausal women with fragility fractures have osteopenia or normal BMD [6] in the United States. Osteoporosis treatments are generally not indicated for fracture prevention in patients with osteopenia based on the current clinical recommendations; thus, a considerable number of women are at risk of fracture.

The prevalence of osteopenia ranges from 27.1% to 51.6%, with a reportedly high prevalence among postmenopausal women in Asian countries, where the population is aging rapidly [7-9]. Meanwhile, there is a demand for ethnic-specific evidence owing to the high heterogeneity in BMD distributions and differential fracture risks across ethnicities [10]. Asian postmenopausal women have the lowest BMD among five different ethnic groups (Asian vs. Caucasian [mean T-score]: -1.22 vs. -0.89) [10]. A longitudinal study from Hong Kong demonstrated that lower BMD was associated with a 1.5-fold and 1.7-fold increased risk of fragility fractures per standard deviation (SD) reduction in BMD at the spine and hip, respectively [11]. However, owing to the limitation of convenience sampling, evidence gaps remain in the assessment of long-term fracture risk in postmenopausal women with osteopenia in the East Asian population.

In South Korea, all women aged 66 years are eligible for BMD analysis through the National Health Screening Program, and their clinical outcomes can be followed for 10 years by retrieving records from the National Health Insurance Database via data linkage. Therefore, we sought to identify the long-term fracture risk over 10 years using BMD measured in a population based screening program.

METHODS

Data source

In South Korea, the National Health Insurance Service (NHIS), a single-payer healthcare system covering the entire population, reimburses costs based on billing records from health care providers. The NHIS launched a national general health screening program for chronic diseases in 1995 [12], followed by the introduction of the National Screening Program for Transitional Ages (NSPTA) in 2007 [13]. The NSPTA examines individuals aged 40 and 66 years, and a complimentary BMD screening is

provided to women aged 66 years as part of the NSPTA [13]. The NHIS informs subjects of their eligibility for the NSPTA screening by sending notification and reminders via post; participants can select sites among the listed healthcare centers or hospitals. Among the individuals who were eligible for the NSPTA health examination, 77% underwent examination in 2015 [14]. Using these data, the NHIS created a database of claims information that encompassed diagnosis records, procedures, surgery, prescriptions, or health screening records.

Furthermore, the NHIS created a database that covered demographic information (age, sex, and income level), national health screening data, and health utilization data (inpatient and outpatient visits, including prescriptions, procedures, and diagnosis records) [15]. The database also contains information on completely enumerated death records obtained from the vital statistics of South Korea. Diagnosis records were coded using the International Classification of Diseases, Tenth Revision (ICD-10). The overall positive predictive value of the diagnoses in the South Korean health insurance claims database was 82% [16]. In the database, each individual has an anonymized unique personal identification number, which enabled individual-level follow-up for 10 years via individual-level linkage across databases (National Health Screening Database, Health Care Utilization Database, and Vital Statistics of Statistics Korea).

The NHIS extracted and provided 50% randomly sampled data from approximately 1 million women aged 66 years who underwent the NSPTA health examination and BMD screening between January 1, 2008, and December 31, 2015. Due to the NHIS's data access policy, a maximum of 50% of randomly selected sample data was available for external researchers due to privacy issues. From the nationwide healthcare claims database, all patients' reimbursed healthcare encounters (including diagnostic records, prescriptions, or procedures) were retrieved, and therefore, longitudinal patient-level follow-up was possible in our study.

Study subjects

We conducted a retrospective cohort study over 10 years, using data from postmenopausal women who underwent BMD screening tests in the NSPTA health examination at the age of 66 years between January 1, 2008, and December 31, 2015. Subjects were followed up until December 31, 2017, to ensure at least 2 years of follow-up.

Exposure

BMD was measured using dual-energy X-ray absorptiometry

(DXA) [17] primarily at the spine; if this was impossible (due to vertebral fracture or surgery), BMD was measured at the femoral neck [18]. The subjects were categorized into normal BMD (T score ≥ -1.0), osteopenia (T-score < -1.0 SD and > -2.5 SD), and osteoporosis (T score ≤ -2.5 SD), according to the World Health Organization (WHO) criteria [19].

Cohort entry was defined as the date of BMD screening. A minimum of 1 year of database history prior to cohort entry was required for all subjects to ascertain study eligibility and to assess baseline demographic and clinical characteristics. The following subjects were excluded (Supplemental Table S1): (1) subjects with a history of cancer, Paget's disease, human immunodeficiency virus (HIV) infection, or osteogenesis imperfecta to exclude the impact of residual confounding from conditions known to be associated with an increased risk of fracture; (2) subjects with a history of fracture or trauma, as these are major and time-dependent risk factors for subsequent fragility fractures; (3) subjects who had chronic exposure to glucocorticoids (≥ 5 mg prednisolone-equivalent steroid/day for ≥ 3 months) to exclude glucocorticoid-induced osteoporosis fracture risk [20]; and (4) subjects who previously received osteoporosis treatment.

This study was approved by the Institutional Review Board of Sungkyunkwan University (approval number: SKKU 2019-02-006). Written informed consent was not applicable, as this study used anonymized subject data.

Outcome

Subjects with an incident fracture event of the vertebrae, hip, or non-hip and non-vertebral (NHNV) sites, as defined in a previous publication by Lee et al. [21], during the follow-up period were considered to develop an outcome (Supplemental Table S1). To ascertain cases of fragility fractures, subjects who experienced any traumatic event were censored at the date the event occurred. Subjects were followed from cohort entry until the outcome of interest (fragility fracture), trauma, death, or end of the study period (December 31, 2017), whichever occurred first. We censored the observation of subjects if any censoring event occurred rather than excluding these subjects at the start of the follow-up because excluding these patients would introduce additional selection bias by using future information to determine the inclusion of study subjects. As our analysis was based on a nationwide healthcare claims database, artificial dropouts due to transfer or referral to different health care providers or patient withdrawal were unlikely to occur.

Potential confounders

We selected potential confounders based on previous literature on the factors associated with fragility fractures [22] and assessed these confounders in the year before cohort entry. Potential confounders included income level, lifestyle (smoking and alcohol consumption frequency), body mass index (BMI; categorized into underweight [< 18.5 kg/m²], normal [18.5–22.9 kg/m²], overweight [23.0–24.9 kg/m²], obese I [25.0–29.9 kg/m²], or obese II [≥ 30.0 kg/m²] according to the Asian criteria of the WHO) [23], baseline clinical conditions, including risk factors for fracture, such as subclinical hyperthyroidism [24], diabetes mellitus [25], hypertension [26], chronic obstructive pulmonary disease (COPD)/asthma [27,28], and rheumatoid arthritis [29] (listed in Supplemental Table S1), and comedications (calcium and vitamin D, anticonvulsants, proton pump inhibitors, thyroid hormones, selective serotonin reuptake inhibitors, and thiazolidinediones). We also assessed the use of osteoporosis medications during the patient follow-up (including oral bisphosphonates [alendronate, risedronate, and ibandronate, with or without vitamin D derivatives], intravenous bisphosphonates [ibandronate, pamidronate, and zoledronate], and selective estrogen receptor modulators [SERMs; raloxifene and bazedoxifene]). Clinical diagnoses were determined and coded according to the ICD-10 by clinicians based on relevant clinical guidelines and clinical judgment. We additionally retrieved data on the conduct of BMD tests within 2 years after cohort entry to assess whether the frequency of subsequent BMD tests was different among the three BMD groups.

Statistical analysis

The demographic and clinical characteristics of the study subjects with normal BMD, osteopenia, or osteoporosis were described. The 10-year cumulative incidence was defined as the number of incident fracture events during the study period divided by the number of persons at risk within the cohort. It represented the proportion of women with new fractures among women at risk over 10 years. Cumulative incidence curves were derived using the Kaplan-Meier approach, presenting the time to incident fracture for all three groups during follow-up. Significance was determined using a log-rank test. We constructed Cox proportional hazard models to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs) for the risk of fracture in subjects with osteopenia or osteoporosis versus those with normal BMD. The outcome models were adjusted for income, smoking, alcohol consumption, BMI, comorbidities (thyroid dysfunction, asthma, COPD, rheumatoid arthritis, hypertension,

myocardial infarction, heart failure, diabetes mellitus, dyslipidemia, stroke, chronic kidney disease, and gastrointestinal disorders) and comedications (thyroid hormones, calcium and vitamin D, anticonvulsants, proton pump inhibitors, selective serotonin reuptake inhibitors, and benzodiazepines). Further analyses were performed to assess the outcomes of each fracture type.

To describe the range of fracture risk among those receiving an osteoporosis treatment or not, we conducted stratified analyses by any use of osteoporosis medication between the BMD screening date and end of follow-up (fracture occurrence, censoring event, or study end date). Moreover, given bone deterioration over time may be high in post-menopausal women, some women with normal or osteopenic baseline BMD may have progressed to osteoporosis over the 10-year follow-up. Thus, to limit this potential misclassification of differences in baseline and subsequent BMD categories during the follow-up period, the analyses were stratified by any use of osteoporosis medications during the follow-up period to capture the patients most likely to have progression to osteoporosis. All statistical analyses were performed using SAS Enterprise Guide version 7.1 for Windows (SAS Institute Inc., Cary, NC, USA). A two-tailed value of $P < 0.05$ indicated significance.

RESULTS

Baseline characteristics

Among 335,363 women who underwent DXA BMD testing

from January 1, 2008, to December 31, 2015, we included 271,197 women after excluding subjects with a history of osteoporosis medication use ($n=26,658$), fracture ($n=19,830$), cancer ($n=15,662$), chronic glucocorticoid use ($n=1,087$), trauma ($n=913$), HIV infection ($n=12$), and Paget's disease ($n=4$). Among 271,197 women who met the eligibility criteria, 56,189 (20.7%) had normal BMD, 119,458 (44.0%) had osteopenia, and 95,550 (35.2%) had osteoporosis, based on their BMD T-scores (Fig. 1). Clinically compared to normal BMD group, osteoporotic patients were less likely to be obese, had generally fewer co-morbidities, and were more likely to receive subsequent BMD test (Table 1).

Fracture risk in different BMD groups

Over a mean follow-up of 4.54 years, 61,671 incident fracture events occurred and over half of the events occurred in women with normal BMD or osteopenia (15.9% and 42.5%, respectively), while 41.6% of the events occurred in women with osteoporosis. The 10-year cumulative incidence of all fractures in postmenopausal women with normal BMD, osteopenia, and osteoporosis was 31.1%, 37.5%, and 44.3%, respectively (Fig. 2A). Likewise, the 10-year cumulative incidence of vertebral fracture was higher in women with osteopenia than in women with normal BMD (10.9% vs. 6.5%) (Fig. 2B), as was the cumulative incidence of hip fracture (2.2% vs. 1.9%) (Fig. 2C) and NHNV fracture (30.7% vs. 26.5%) (Fig. 2D). The cumulative incidence of fracture among women with osteoporosis was largely com-

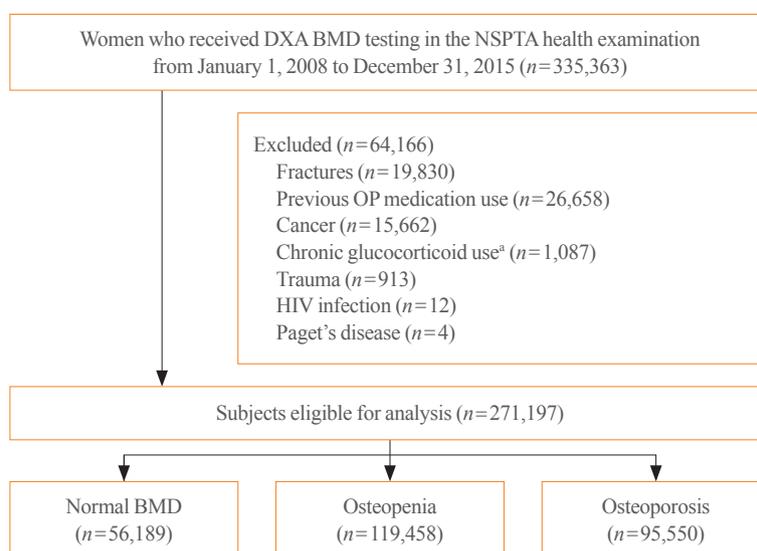


Fig. 1. Selection of study subjects who underwent dual-energy X-ray absorptiometry (DXA) bone mineral density (BMD) screening from the National Screening Program for Transitional Ages (NSPTA). OP, osteoporosis; HIV, human immunodeficiency virus. ^a ≥ 5 mg prednisolone-equivalent steroid/day for ≥ 3 months.

Table 1. Characteristics of Postmenopausal Women with Normal BMD, Osteopenia, or Osteoporosis Who Underwent the Nationwide DXA BMD Screening Test (2008–2015)

Characteristic ^a	Normal BMD (n=56,189)	Osteopenia (n=119,458)	Osteoporosis (n=95,550)
BMI			
Underweight (<18.5 kg/m ²)	280 (0.5)	1,149 (1.0)	2,855 (3.0)
Normal (18.5–22.9 kg/m ²)	11,679 (20.8)	32,876 (27.5)	35,604 (37.3)
Overweight (23.0–24.9 kg/m ²)	14,389 (25.6)	32,818 (27.5)	25,639 (26.8)
Obese I (25.0–29.9 kg/m ²)	24,998 (44.5)	46,326 (38.8)	28,487 (29.8)
Obese II (≥30.0 kg/m ²)	4,833 (8.6)	6,268 (5.3)	2,942 (3.1)
Smoking			
Never	49,625 (88.3)	104,882 (87.8)	82,902 (86.8)
Past but stopped	616 (1.1)	1,191 (1.0)	802 (0.8)
Current	847 (1.5)	1,846 (1.6)	1,929 (2.0)
Alcohol consumption (≥1 time per week)	4,477 (8.0)	8,980 (7.5)	6,421 (6.7)
Baseline clinical condition			
Hypothyroidism	3,419 (6.1)	6,380 (5.3)	4,330 (4.5)
Hyperthyroidism	1,140 (2.0)	2,465 (2.1)	1,786 (1.9)
Other thyroid disorder	4,934 (8.8)	9,808 (8.2)	6,831 (7.2)
Asthma	8,014 (14.3)	16,647 (13.9)	12,517 (13.1)
COPD	10,430 (18.6)	21,401 (17.9)	15,300 (16.0)
Rheumatoid arthritis	2,913 (5.2)	5,709 (4.8)	3,872 (4.1)
Hypertension	30,919 (55.0)	58,918 (49.3)	40,708 (42.6)
Diabetes mellitus	15,226 (27.1)	27,597 (23.1)	17,893 (18.7)
Dyslipidemia	25,330 (45.1)	49,222 (41.2)	32,760 (34.3)
Stroke	3,682 (6.55)	7,624 (6.38)	5,744 (6.0)
Chronic kidney disease	348 (0.6)	700 (0.6)	513 (0.5)
Previous medication use			
Thyroid hormones	2,295 (4.1)	4,259 (3.6)	2,759 (2.9)
Calcium and vitamin D	4,227 (7.5)	12,796 (10.7)	9,914 (10.4)
Subsequent BMD test within 2 years after cohort entry			
Yes	15,081 (26.8)	37,104 (31.1)	40,860 (42.8)

Values are expressed as number (%).

BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

^aAll variables were nominally statistically different ($P<0.01$) among the three cohorts with exception to chronic kidney disease.

parable to that among women with osteopenia. The risk of fragility fractures was higher in women with osteopenia than in women with normal BMD (HR, 1.31; 95% CI, 1.28 to 1.34) (Table 2). Similar results were observed for women with osteoporosis when compared with women with normal BMD (HR, 1.68; 95% CI, 1.64 to 1.72).

Table 3 shows the risk of overall fracture stratified by any use of osteoporosis treatment during the follow-up. Consistent with the major findings, the association between baseline BMD group and fracture risk remained consistent where the incidence was the highest among osteoporosis, followed by osteopenia

and normal BMD group in both treated and non-treated groups. Among women who initiated an osteoporosis treatment during follow-up, overall fracture incidence rates per 100 person-years (PY) were 2.92, 3.41, and 4.88 in women with normal BMD, osteopenia, and osteoporosis, respectively. On the other hand, the overall fracture incidence rates per 100 PY among those who did not receive osteoporosis treatment during follow-up were 3.92, 5.50, and 8.09 in women with normal BMD, osteopenia, and osteoporosis, respectively. Among women diagnosed with osteoporosis at the index screening, 59.8% initiated an osteoporosis treatment during follow-up and their 10-year cumu-

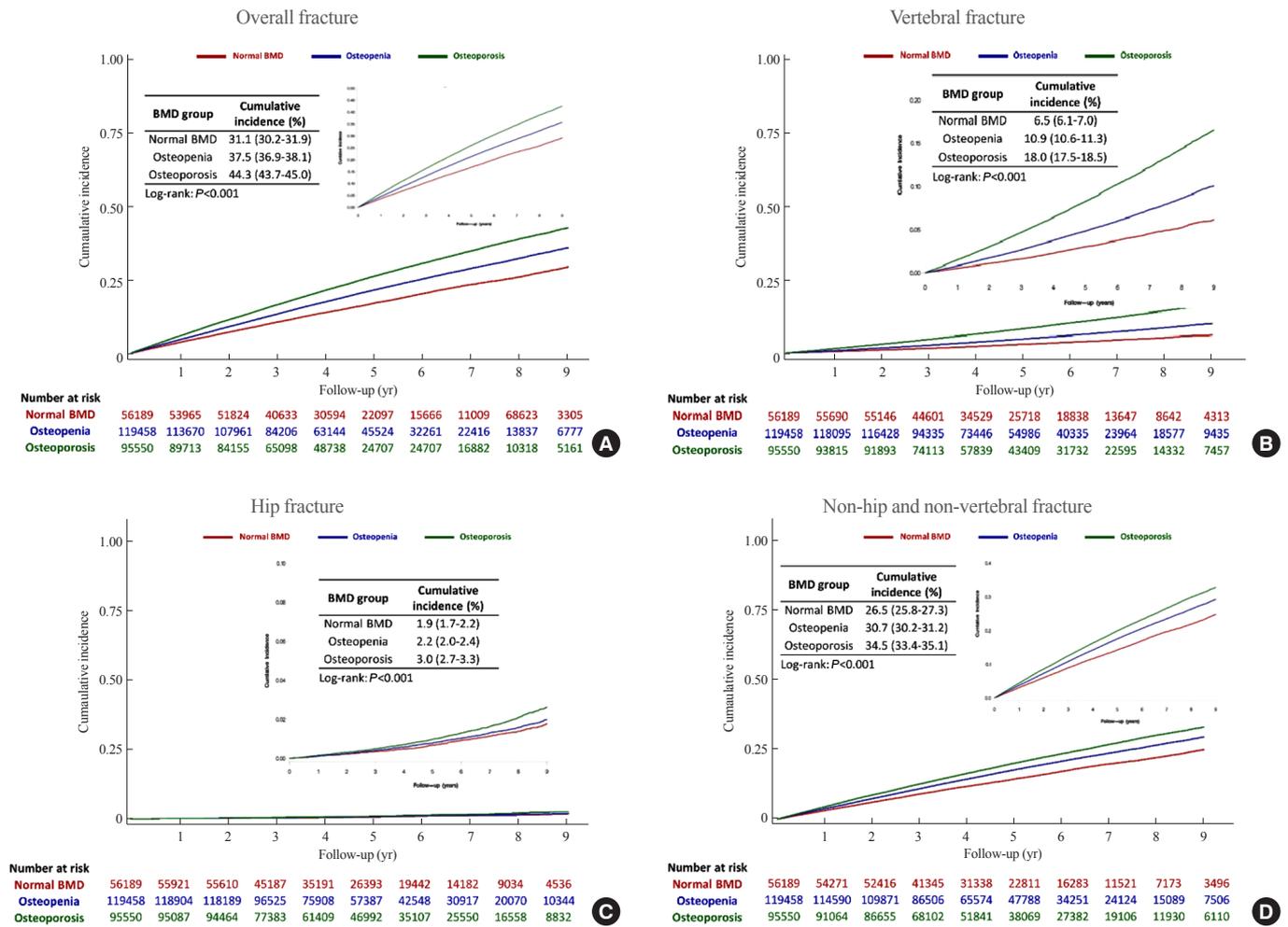


Fig. 2. Cumulative incidence curves for the time to (A) overall, (B) vertebral, (C) hip, and (D) non-hip and non-vertebral fractures after dual-energy X-ray absorptiometry (DXA) bone mineral density (BMD) screening test in subjects with normal BMD, osteopenia, or osteoporosis.

lative incidence was 38.3%; 41.2% did not initiate an osteoporosis treatment during follow-up and their 10-year cumulative incidence was 48.9%. While similar trends were observed in the analyses stratified by fracture subtypes (Supplemental Tables S2-S4), the incidence of hip fracture did not differ between normal and osteopenia group among the treated subgroup. The 10-year cumulative incidence of fracture among women with normal and osteopenia baseline BMD who did not receive osteoporosis treatment was 29.4% and 37.8%, respectively. Censoring frequency due to the occurrence of trauma or death was largely similar across the BMD groups (Supplemental Table S5).

DISCUSSION

We conducted a large population-based cohort study to analyze postmenopausal fracture risk in South Korea. Long-term frac-

ture risk was substantial among 271,197 postmenopausal women in South Korea. Following the national screening, the 10-year cumulative fracture incidence in women with normal BMD was 31.1%, while 37.5% and 44.3% in women with osteopenia and osteoporosis, respectively. Although the fracture rate was the highest in women with osteoporosis, over half of the fracture events that occurred throughout the 10-year follow-up period were in women with osteopenia or normal BMD. Postmenopausal women with osteopenia had a 1.31-fold increased risk of overall fracture compared with women with normal BMD, independent of other risk factors, including medical history and comedication use. The national BMD screening program in South Korea provided useful insights into identifying postmenopausal women at an increased risk of fracture.

Consistent with our findings, where most fractures occurred in postmenopausal women with modest BMD (T-score >-2.5

Table 2. Risk of Fracture in Subjects with Osteopenia or Osteoporosis versus Subjects with Normal BMD

Fracture site	No. of subjects	No. of events	PY at risk	Incidence rate per 100 PY (95% CI) ^a	Unadjusted HR (95% CI)	Adjusted HR (95% CI) ^b
Overall fracture						
Normal BMD	56,189	9,804	262,170	3.74 (3.67–3.81)	Ref (1.00)	Ref (1.00)
Osteopenia	119,458	26,223	545,481	4.81 (4.75–4.86)	1.29 (1.26–1.32)	1.31 (1.28–1.34)
Osteoporosis	95,550	25,644	424,087	6.05 (5.98–6.12)	1.62 (1.58–1.66)	1.68 (1.64–1.72)
Vertebral fracture						
Normal BMD	56,189	1,819	287,386	0.63 (0.6–0.66)	Ref (1.00)	Ref (1.00)
Osteopenia	119,458	6,402	610,324	1.05 (1.02–1.07)	1.66 (1.57–1.75)	1.71 (1.62–1.80)
Osteoporosis	95,550	8,746	481,328	1.82 (1.78–1.86)	2.87 (2.73–3.02)	3.09 (2.94–3.25)
Hip fracture						
Normal BMD	56,189	451	291,800	0.15 (0.14–0.17)	Ref (1.00)	Ref (1.00)
Osteopenia	119,458	1,119	626,618	0.18 (0.17–0.19)	1.15 (1.03–1.28)	1.20 (1.07–1.34)
Osteoporosis	95,550	1,158	505,568	0.23 (0.22–0.24)	1.47 (1.32–1.64)	1.59 (1.42–1.78)
NHNV fracture						
Normal BMD	56,189	8,323	266,931	3.12 (3.05–3.18)	Ref (1.00)	Ref (1.00)
Osteopenia	119,458	21,532	561,106	3.84 (3.79–3.89)	1.23 (1.20–1.26)	1.24 (1.21–1.27)
Osteoporosis	95,550	19,716	444,466	4.44 (4.38–4.5)	1.42 (1.39–1.46)	1.46 (1.42–1.50)

PY, person-years; CI, confidence interval; HR, hazard ratio; BMD, bone mineral density; NHNV, non-hip and non-vertebral.

^aIncidence rate per 100 person-years=(number of incident fracture events/person-years at risk)×100; ^bAdjusted for income, smoking, alcohol consumption, body mass index, comorbidities (thyroid dysfunction, asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, hypertension, myocardial infarction, heart failure, diabetes mellitus, dyslipidemia, stroke, chronic kidney disease, gastrointestinal disorders) and comedications (thyroid hormones, calcium and vitamin D, anticonvulsants, proton pump inhibitors, selective serotonin reuptake inhibitors, and benzodiazepines).

Table 3. Risk of Overall Fracture Stratified by the Use of Osteoporosis Treatment during the Follow-up in Subjects with Osteopenia or Osteoporosis versus Subjects with Normal BMD

Stratification	No. of subjects	No. of events	PY at risk	10-Year cumulative incidence, %	Incidence rate per 100 PY (95% CI) ^a	Crude HR (95% CI)	Adjusted HR (95% CI) ^b
With any osteoporosis treatment use during follow-up^c							
Normal	8,067	1,359	46,574	26.5	2.92 (2.77–3.07)	Ref (1.00)	Ref (1.00)
Osteopenia	33,657	6,191	181,420	30.3	3.41 (3.33–3.50)	1.19 (1.12–1.26)	1.21 (1.14–1.29)
Osteoporosis	57,120	13,178	270,059	38.3	4.88 (4.80–4.96)	1.75 (1.66–1.86)	1.85 (1.74–1.95)
Without any osteoporosis treatment use during follow-up							
Normal	48,122	8,445	215,596	29.4	3.92 (3.84–4.00)	Ref (1.00)	Ref (1.00)
Osteopenia	85,801	20,032	364,061	37.8	5.50 (5.43–5.58)	1.40 (1.37–1.44)	1.43 (1.40–1.47)
Osteoporosis	38,430	12,466	154,028	48.9	8.09 (7.96–8.23)	2.06 (2.00–2.12)	2.17 (2.11–2.23)

BMD, bone mineral density; PY, person-years; CI, confidence interval; HR, hazard ratio.

^aIncidence rate per 100 person-years=(number of incident fracture events/person-years at risk)×100; ^bAdjusted for income, smoking, alcohol consumption, body mass index, comorbidities (thyroid dysfunction, asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, hypertension, myocardial infarction, heart failure, diabetes mellitus, dyslipidemia, stroke, chronic kidney disease, gastrointestinal disorders) and comedications (thyroid hormones, calcium and vitamin D, anticonvulsants, proton pump inhibitors, selective serotonin reuptake inhibitors, and benzodiazepines); ^cOsteoporosis treatment status was ascertained between the index BMD screening date and end of follow-up (fracture occurrence, censoring event, or study end date).

SD), 82% and 73% of fractures occurred in women with osteopenia and normal BMD in the United States [6] and Australia [30], respectively. Although differences in demographics across the BMD groups precluded a direct comparison, osteopenia and osteoporosis were more prevalent in our data (44.0% and 35.2%, respectively) than in a study of postmenopausal women from the United States (51.4% and 15.4%) [31] and Australia (48.0% and 14.5%) [30], most of whom were Caucasian [11]. We observed higher fracture incidences per 100 PY in the normal BMD and osteopenia groups (4.81 and 6.05, respectively) compared with those in Danish women (3.55 and 4.74, respectively) [32].

In the Asian population, a study conducted in Hong Kong predicted the 10-year incidence of fragility fracture risk in women (mean age, 63.4 years) recruited from 1995 to 2002 [11]. The 10-year cumulative incidence in our study was higher than the predicted 10-year absolute risk in women from Hong Kong with three to eight other clinical risk factors (the predicted 10-year fracture incidence for normal BMD, osteopenia, and osteoporosis in Hong Kong were 13%, 23.4%, and 30%, respectively) [11]. This discrepancy in the 10-year fracture risk between South Korea and Hong Kong may have occurred because of the exclusion of women with a personal/family history of osteoporosis, other bone-related disorders, and premature menopause (age <40 years) in the Hong Kong study, resulting in healthier study participants relative to postmenopausal women in East Asia overall [11,33]. We observed a similar vertebral fracture incidence compared with that in Japanese women (mean age, 65.0 years) from the regional health screening data between 1994 and 1995 (incidence per 100 PY in South Korea vs. Japan: 1.23 vs. 1.24) [34]. Hip fracture incidence per 100 PY was higher or comparable with our results in China, Hong Kong, and Taiwan (0.18 [35], 0.27 [36], and 0.51 [37], respectively). Therefore, our results confirm that postmenopausal fracture risk is still substantial in Asia, despite advances in diagnosis and preventive treatments in recent years.

Global epidemiological data suggest that the burden of fragility fractures remains a major public health issue in Asia owing to the forecasted rapid aging of the population in the upcoming decades [38]. However, fragility fractures have practical opportunities for disease prevention and modification by implementation of population-driven preventive strategies and early identification of at-risk individuals. Even a small increase in bone mass may markedly reduce the burden of fractures at a population level; randomized trials of antiresorptive agents demonstrated a 35% to 50% reduction in fracture risk with a 1% to 6%

improvement in spine BMD [39]. While the study was not designed specifically to measure the effectiveness of treatment, we observed that osteoporotic women who initiated an osteoporosis treatment during follow-up had a lower 10-year cumulative incidence of fracture than did the non-treated women. This difference could either be reflective of therapy or the type of patients who started therapy. While similar trends indicating the correlation between baseline BMD and fracture risk were observed in the analyses stratified by fracture subtypes, the incidence of hip fracture did not differ between normal and osteopenia group among the treated subgroup. These results may have been affected by the time-varying effect of external risk factors for fracture during the follow-up, or, alternatively, it may reflect the limitation of using spine BMD to predict the risk of hip fracture.

The population-based screening program in South Korea has a valuable predictive role—identifying subjects with low bone mass and providing an index for the prediction of long-term fracture risk. In these national BMD screening data, 58.4% of women who developed fragility fractures had baseline BMD T-scores >−2.5. While the magnitude of fracture risk was substantial among women in the osteopenia range, these patients were not necessarily recommended pharmacologic interventions unless they had a history of fracture, ≥20% fracture risk assessment tool 10-year probability of major fragility fracture, or ≥3% 10-year probability of hip fracture [16,40,41]. A recent update in the South Korean health insurance plan extended the reimbursement coverage of bisphosphonates, SERM, and active vitamin D3 to those who had recent fragility fractures or women with osteopenia who had >90 days of exposure to glucocorticoids within the past 6 months [42]. However, the majority of women with osteopenia without such conditions are not indicated for these treatments according to the current reimbursement criteria. Subsequently, the BMD rescreening rate was not sufficiently high compared with the recommendation of the United States Preventive Services Task Force, suggesting BMD screening for women aged ≥65 years [43]. Therefore, there is an unmet public health need for targeted efforts toward the early identification and treatment of women with osteopenic BMD who have a high risk of fracture.

Our study has several strengths. Our study provides long-term epidemiological evidence indicating that the magnitude of fracture risk in the Asian population is substantial. To our knowledge, this is the largest population based study to examine postmenopausal fragility fracture risk in an Asian population. Due to our use of a nationwide healthcare claims database, all subjects' reimbursed healthcare encounters (including diagnostic records,

prescriptions, or procedures) were retrieved, and therefore, artificial follow-up loss due to a transfer to a different health care provider or death is unlikely to have occurred in our study. In contrast, artificial follow-up loss is a frequent source of outcome misclassification bias in previous studies using survey data or electronic health records, which may lead to under-detection of study outcomes. The artificial follow-up loss may also give rise to selection bias, given that patients with an incomplete follow-up due to transfer to advance healthcare centers (e.g., long-term nursing facilities) are likely to have differential clinical characteristics to those who remained in the study cohort. Furthermore, our findings have solid external validity because of the assembly of data from a nationwide screening program in which the study subjects were followed longitudinally.

However, our study has several limitations. First, this study has a potential limitation of misclassification of BMD group. As we used lumbar spine BMD values from national health screening, osteoporotic patients with low hip BMD may have been included in the osteopenia group. It is possible that the study subjects with osteoporotic cortical BMD, but with osteopenic trabecular BMD, were defined as osteopenia group. With the use of spine BMD testing results, the risk for vertebral fractures could differ the most, and these results also show the predictive role of spine BMD for hip or NHNV fractures. The plausible reason could be that trabecular BMD may serve as a proxy marker for the overall decrease in BMD because trabecular bone responds to metabolic changes more sensitively than does cortical bone [44]. Second, the data were primarily collected for health insurance claims for reimbursement purposes; thus, the inherent limitation of health insurance claims data may exist in the form of incomplete, inaccurate, or missing data [45]. The prevalence of baseline clinical characteristics may have been affected by the potential miscoding of diagnostic codes. A validation study comparing the diagnosis records of the South Korean healthcare database with electronic medical records indicated an overall positive predictive value of 82% [16]. Third, only a one-time BMD measurement at the age of 66 years was available, and we could not observe BMD changes during the follow-up period. Fourth, it is unclear whether post-diagnostic procedures, such as patient counseling and education [46], were implemented in subjects with osteopenia or osteoporosis, and the consequences of these interventions were not quantified. Information on medication intake for patients with osteopenia was unavailable in this database, as it is not reimbursed by the NHIS in Korea. Fifth, we cannot exclude the possibility that results from BMD screening and clinical diagnosis of osteoporosis and os-

teopenia can be different, although BMD screening is considered the most commonly used indicator. Finally, not all relevant data are available within the data source. Of 10 risk factors for fracture that are commonly considered in clinical practice [47], the data source for this study had data on eight risk factors (covariates of age, sex, systemic glucocorticoid use, rheumatoid arthritis diagnosis, prior fracture, BMI, alcohol use, smoking status), but did not include data on the other two risk factors (femoral neck BMD, and parental history of fracture).

In conclusion, the long-term fracture risk in postmenopausal women is substantial in patients with osteopenia and osteoporosis. Despite advances in diagnosis and preventive treatments implemented in recent years, recommendations and guidelines for post-BMD screening still need to be improved. In addition, it is important to note that over half of the fractures within 10 years occurred in women with modestly reduced BMD, including women with osteopenia, which warrants targeted efforts toward early identification and implementation of preventive strategies for women who are in the osteopenia range but at a high risk of fracture. This study supports the notion that public health policy should aim to reduce the burden of fragility fractures.

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception or design: Y.H.B., S.W.C., Y.H., J.L.L., J.Y.S. Acquisition, analysis, or interpretation of data: Y.H.B., S.W.C., H.E.J., J.H.K., Y.H., J.L.L., J.Y.S. Drafting the work or revising: Y.H.B., S.W.C., H.E.J., J.H.K., Y.H., J.L.L., J.Y.S. Final approval of the manuscript: Y.H.B., S.W.C., H.E.J., J.H.K., Y.H., J.L.L., J.Y.S.

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