



More evidence to support a lower quantitative computed tomography (QCT) lumbar spine bone mineral density (BMD) cutpoint value for classifying osteoporosis among older East Asian women than for Caucasians

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Introduction

Quantitative computed tomography (QCT) for bone mineral density (BMD) measurement can be performed on any CT scanner with the use of a calibration phantom. Calibration phantoms are required to transform the attenuation measured in Hounsfield units into a BMD value in units of mg/mL. It is expected that the application of QCT for spine BMD will increase, particularly in the setting of opportunistic screening. The most common form of QCT provides a trabecular bone measurement (1-4). Numerous studies have demonstrated that the skeleton of East Asians has microstructural and mechanical advantages (5,6). For example, Walker *et al.* (7,8) reported that postmenopausal Chinese women have a higher trabecular plate-to-rod ratio and greater whole bone stiffness, translating into greater trabecular mechanical competence despite smaller bone size compared to Caucasian women. For the spine, compared with older

Caucasian women, older Chinese women are less likely to have disc space narrowing, thoracic spine hyper-kyphosis, vertebral osteoarthritic wedging, Schmorl nodes defect, and degenerative spondylolisthesis (9,10). Almost all of the published results comparing East Asians and Caucasians show nearly all fragility fracture prevalences, including hip fracture, vertebral fracture, humerus fracture, and wrist fracture, are no more than half that of older Caucasians, both for men and women [reviewed in (11,12)].

For Caucasian women (and men), the recommended QCT lumbar spine (LS) trabecular BMD cutoff value for osteoporosis is 80 mg/mL (13,14). The same QCT criterion has also been commonly applied to East Asian populations (15-23), despite earlier reports that East Asian women suffer from vertebral fragility fracture at a lower LS QCT BMD than Caucasian women (24,25). Considering the different bone properties and the much lower incidence of fragility fractures in East Asian women compared with Caucasians

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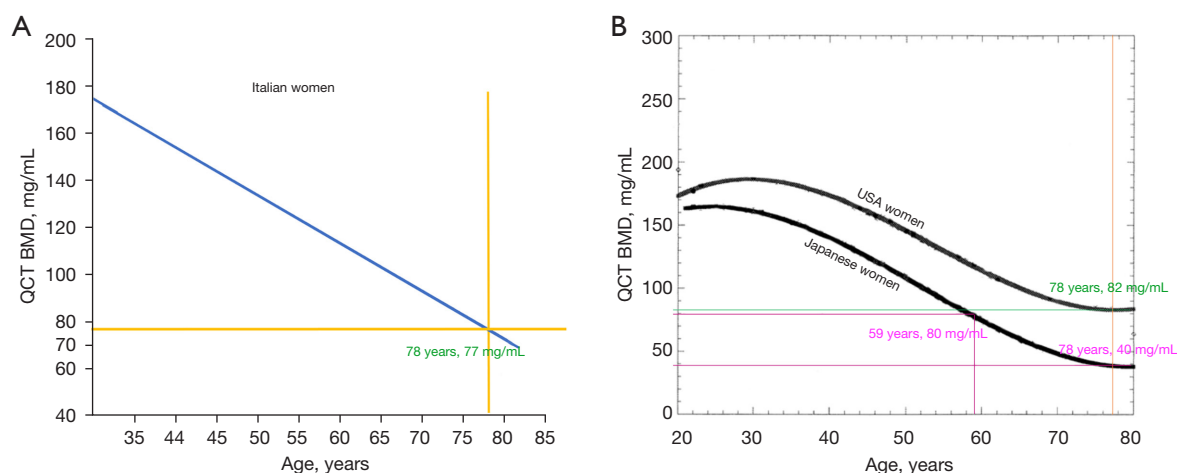


Figure 1 Women's population mean LS QCT BMD decreases during aging. (A) For Italian women at the age of 78 years, the mean LS BMD decreases to around 77 mg/mL. (B) For USA women at the age of 78 years, the mean LS BMD decreases to around 82 mg/mL. For Japanese women at the age of 78 years, the mean LS BMD decreases to around 40 mg/mL, while for a mean BMD value of 80 mg/mL, the corresponding age is 59 years. Data in (A) from Guglielmi *et al.* (33); Japanese data in (B) from Ito *et al.* (25); US women's data (assumed predominantly Caucasians) from Block *et al.* (31) and Ito *et al.* (25). The values in (B) for US subjects and for Japanese subjects had been cross-validated. QCT, quantitative computed tomography; BMD, bone mineral density; LS, lumbar spine.

(26–28), based on literature evidence, we recently argued that the QCT LS BMD equivalent to the older Caucasian women's threshold of 80 mg/mL is about 45–50 mg/mL for East Asian women (29). To strengthen that argument, in this article, we list more evidence.

East Asian women have a lower QCT LS BMD with aging than Caucasians

We have previously noted that, for US Caucasian women aged 78 years, based on the data of Looker *et al.* (30) and Block *et al.* (31), the population mean LS dual-energy X-ray absorptiometry (DXA) T-score is -2.5 and QCT BMD is around 80 mg/mL (29). Therefore, on the assumption that BMD measurements are normally distributed, half of them will have densitometric osteoporosis. At the same age, the LS average DXA T-score for Chinese women is -3.7 , which is the recommended threshold to diagnose osteoporosis in Chinese women (28,32). For Chinese and Japanese women at the same age, the QCT LS BMD decreases to an average of around 50 mg/mL, according to the data of Li *et al.* (16) and Fujii *et al.* (24). According to these latter studies, if a QCT LS BMD of 80 mg/mL is used as the cutpoint value to classify osteoporosis, then around half of the Chinese and Japanese female population will be classified as osteoporotic at the age of around 65 years, leading to

serious overdiagnosis (12,28,29).

In this article, we list more literature data to support this observation. *Figure 1A* shows that, for Italian women at the age of 78 years, the mean QCT LS BMD has decreased to around 77 mg/mL (33), which is consistent with the data of Block *et al.* (31). This conclusion is supported by many other reports for Caucasian women, including Compston *et al.* (34), Sandor *et al.* (35), and Karantanas *et al.* (36), and Manisal *et al.* (37). *Figure 1B* compares data of US women by Block *et al.* (31) and Japanese women by Ito *et al.* (25). For Japanese women at the age of 78 years, the mean QCT LS BMD has decreased to around 40 mg/mL, which is consistent with the data of Fujii *et al.* (24). For a BMD value of 80 mg/mL, according to the same study, for Japanese women, the corresponding age would be less than 60 years. *Figure 2A* shows that, for Korean women at the age of 78 years, the mean QCT LS BMD decreases to around 50 mg/mL, while for a mean BMD value of 80 mg/mL, the corresponding age is around 67 years (38). *Figure 2B* shows that, for Thai women at the age of 78 years, the mean QCT LS BMD decreases to less than 45 mg/mL, while for a BMD value of 80 mg/mL, the corresponding age is around 67 years (39). These QCT LS BMD results for older East Asian women are consistent with many other studies conducted on Chinese women (40–43). For example, Zhang *et al.* (40) reported a study of healthy subjects in which the

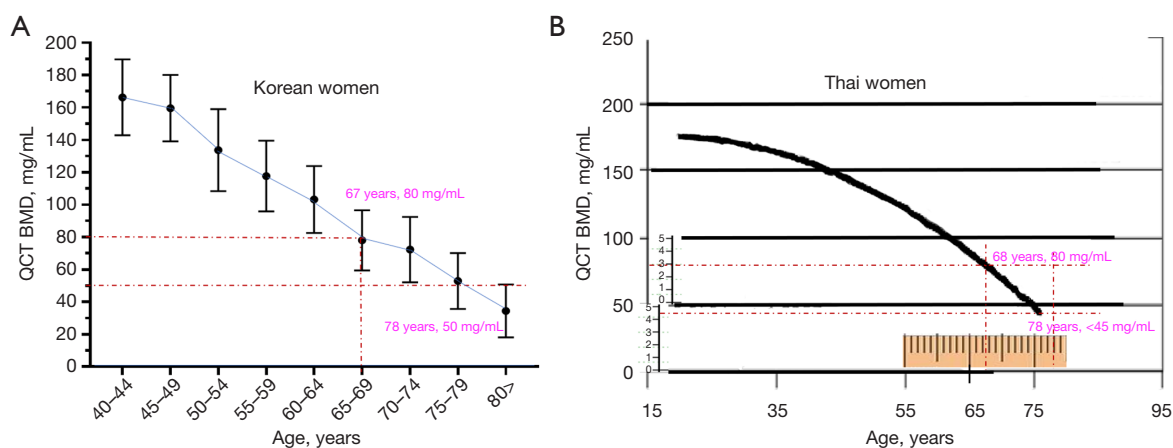


Figure 2 During aging of Korean (A) and Thai (B) women, the population mean LS QCT BMD decreased. (A) For Korean women at the age of 78 years, the mean LS BMD decreases to around 50 mg/mL, while for a BMD value of 80 mg/mL, the corresponding age is around 67 years. (B) For Thai women at the age of 78 years, the mean LS BMD decreased to less than 45 mg/mL, while for a BMD value of 80 mg/mL, the corresponding age is around 68 years. Data in (A) is from Youn and Kim (38). Data in (B) is from Hoonpongsimanon *et al.* (39). QCT, quantitative computed tomography; BMD, bone mineral density; LS, lumbar spine.

mean QCT LS BMD was 82.39 ± 27.45 mg/mL for females aged 60–69 years and 63.78 ± 30.59 mg/mL for females aged ≥ 70 years. In a group of healthcheck women, Xuan *et al.* (41) reported that the mean QCT LS MBD was 63.9 ± 29.7 mg/mL for older participants (>60 years). Similarly, in a group of BMD examinees (excluding those with disorders or medication histories that can affect bone metabolism), Wang *et al.* (42) reported that the mean QCT LS MBD was 62.4 ± 28.3 mg/mL for older female participants (>60 years). Hsu *et al.* (43) studied abdominal CT scan examinees (excluding those with disorders or medication histories that can affect bone metabolism). At the age of 63 years, the mean QCT LS MBD was around 80 mg/mL for their female participants. Moreover, Melton *et al.* (44) reported that, at the age of 62 years, the mean QCT LS BMD of Vietnamese women in the US was 26 mg/mL less than that of US Caucasian women.

It is also well established that peak LS BMD is lower among East Asian women than Caucasian women (12,24,25,45).

Note that, at the age of 78 years, the fragility fracture risk of Chinese and Japanese women is still lower than that of Caucasian women of the same age. Therefore, the data in Figures 1,2 support the conclusion that, for older East Asian women, the threshold for the QCT LS BMD definition of osteoporosis equivalent to the Caucasian women's threshold of 80 mg/mL is no more than 50 mg/mL.

Older Chinese women experience vertebral fracture at a lower QCT LS BMD than Italian women: a comparison with spine fracture severity as the reference

Among Caucasian women, the lifetime risk of hip fracture at the age of 50 years is considered to be around 16%. According to the WHO criteria, the T-score is defined as: $(\text{BMD}_{\text{patient}} - \text{BMD}_{\text{young normal mean}}) / \text{SD}_{\text{young normal population}}$. In Caucasian women aged ≥ 50 years, a cutpoint value of femoral neck BMD 2.5 SD below $\text{BMD}_{\text{young normal mean}}$ results in a prevalence of densitometrically defined osteoporosis of about 16.2%, similar to the lifetime risk of hip fragility fracture. Following a line of thinking similar to the WHO definition of osteoporosis, we performed a study to determine what proportion of older community women with what severity of radiographic osteoporotic vertebral fracture correspond to what low T-score status (46). All the data are from the “Osteoporotic Fracture in Women (Hong Kong)” study and the “Roman Osteoporosis Prevention Project”. The recruitment plan was designed so that the participants would represent the older general population in the correct proportion by age. For the current analysis, we included 301 Italian women with a mean age of 73.6 ± 6.1 years, and 512 Chinese women with a mean age of 74.0 ± 7.2 years. The T4–L5 vertebrae were evaluated with an extended version of the semi-quantitative criteria (eSQ) (47).

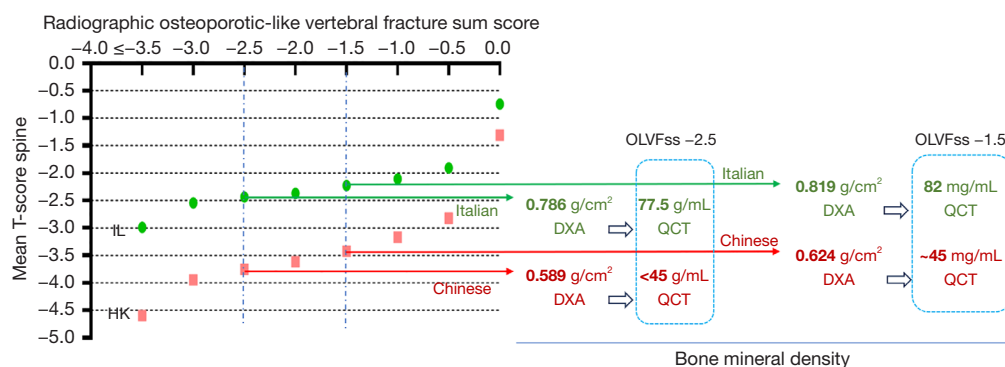


Figure 3 Relationship between OLVF severity and BMD for Caucasian Italian women (IL, age: 73.6 ± 6.1 years) and Hong Kong Chinese women (HK, 74.0 ± 7.2 years). Each vertebra on a spine radiograph was assigned a score of 0, -0.5, -1, -1.5, -2, -2.5, or -3 for no radiographic OLVF or OLVFs of <20%, 20–25%, $\geq 25\%$ –1/3, $\geq 1/3$ –40%, $\geq 40\%$ –2/3, and $\geq 2/3$ vertebral height loss, respectively. OLVFss for each subject was calculated by summing the scores of all vertebrae from T4 to L5. Counting each study case, the OLVFss and lumbar T-score were ranked from the smallest negative value to the largest value and plotted on the X- and Y-axes, respectively. When the OLVF is -1.5 and -2.5, for Italian women, the corresponding lumbar spine DXA BMD is 0.819 and 0.786 g/cm², and the corresponding QCT BMD is 82 and 77.5 mg/mL QCT, respectively. For Chinese women, the corresponding lumbar spine DXA BMD is 0.624 and 0.589 g/cm², and the QCT BMD is around 45 and <45 mg/mL QCT, respectively. OLVFss, OLVF sum score; DXA, dual-energy X-ray absorptiometry; QCT, quantitative computed tomography; OLVF, osteoporotic-like vertebral fracture; BMD, bone mineral density.

For each vertebra in women, a score of 0, -0.5, -1, -1.5, -2, -2.5, or -3 was assigned for no osteoporotic-like vertebral fracture (OLVF) or OLVF of <20%, ≥ 20 –25%, $\geq 25\%$ –1/3, $\geq 1/3$ –40%, $\geq 40\%$ –2/3, and $\geq 2/3$ vertebral height loss, respectively. The term OLVF is used because based on a radiograph it is not always possible to diagnose with certainty a vertebral fracture being of osteoporotic cause. An OLVF sum score (OLVFss), which sums the scores of the T4–L5 vertebrae, was calculated for each study subject (46). Hong Kong local BMD reference data and BMD reference values collected in NHANES 2005–2010 were used for the T-score calculation for Chinese and Italians, respectively.

Counting each study case, the OLVFss and lumbar T-score were ranked from the smallest negative value to the largest value and plotted on the X- and Y-axes, respectively (Figure 3). When the OLVF is -1.5, statistically, the corresponding LS T-score is -2.23 for Italian and -3.42 for Chinese women. Based on the original data, the corresponding LS DXA BMDs are 0.819 and 0.624 g/cm², respectively. When the OLVF is -2.5, the corresponding LS T-score is -2.44 for Italian and -3.75 for Chinese women, and the corresponding LS DXA BMDs are 0.786 and 0.589 g/cm², respectively. For Italian women, DXA LS

BMDs of 0.819 and 0.786 g/cm² are equivalent to QCT LS BMDs of around 82 and 77.5 mg/mL, respectively (48–51). Based on the data of Lin *et al.* (17) and Yu *et al.* (52) and supported by the data of Uemura *et al.* (22), for Chinese women, a DXA LS BMD of 0.624 g/cm² is equivalent to a QCT value of around 45 mg/mL, and 0.589 g/cm² is equivalent to less than 45 mg/mL QCT value [see Figure 3 in reference (29)].

To achieve the detection sensitivity of 78% for patients with radiographic OLVF, 90 mg/mL QCT LS BMD for Caucasian women is equivalent to around 60 mg/mL for East Asian women

In addition to Figure 4 presented in reference (29), in this article, we list more data to support our contention that a QCT LS BMD of 80 mg/mL in Caucasian women is equivalent to 45–50 mg/mL in East Asian women. We calculated the QCT LS BMD threshold to achieve a sensitivity of 78% for detecting radiographic OLVF in Caucasian and East Asian women, and the results are shown in Table 1 (17,25,38,48,53–58). The calculations in Table 1 assumed that the respective BMD values are normally distributed. For Caucasian women, the goal was to

Table 1 Caucasian women and East Asian women QCT lumbar spine BMD to detect radiographic OLVF with a sensitivity of around 78%

Authors	Non-OLVF		OLVF		QCT BMD (mg/mL)	Sensitivity (%) [*]
	n	Age (years)	n	Age (years)		
Caucasian women						
Jergas <i>et al.</i> (53)	56	68.0±6.1	55	67.9±6.5	<95.0	78.2
Lang <i>et al.</i> (48)	45	71.5±4.4	26	76.1±6.5	<84.7	76.9
Duboeuf <i>et al.</i> (54)	83	63.6	29	66.6	<89.5	79.3
Cann <i>et al.</i> (55)	20	57.1±10.1	91	62.8±8.0	<87.5	78.0
Andresen <i>et al.</i> (56)	229 women, 17 men, 57.4 (33–87)				<101.9	77.9
East Asian women						
Ito <i>et al.</i> (25)	118	64.3±2.6	67	64.9±6.9	<63.5	77.3
Youn <i>et al.</i> (38)	290	61.9±6.3	34	70.4±7.1	<59.9	76.5
Lin <i>et al.</i> (17)	296 [†]	65.4±9	205 [‡]	72.5±9.7	<62.9	77.6
Qin <i>et al.</i> (57)	80	50–70	80	50–70	<48.1	77.5
Mao <i>et al.</i> (58)	198	68 (61–75)	198	68 (61–75)	<50.6	77.8
Mao <i>et al.</i> (58)	198	68 (61–75)	198	68 (61–75)	<55.6 [§]	75.3 [§]

Age data are represented as mean ± standard deviation or mean and range. *, simulated results assuming normal distribution of QCT BMD data; †, 74.3% female; ‡, 85.4% female; §, calculated with actual data. Results of Cann *et al.* were based on Fig. 6 in reference (55) (Cann *et al.*). QCT, quantitative computed tomography; BMD, bone mineral density; OLVF, osteoporotic-like vertebral fracture.

use data other than those listed in Figure 4 of reference (29). For East Asians, only limited data has been published. Besides the data of Mao *et al.* (58), which are already listed in Figure 4 of reference (29), we additionally included the data of Lin *et al.* (17), Ito *et al.* (25), Youn *et al.* (38), and Qin *et al.* (57). Despite the subjectivity of classifying OLVF, the small size of almost all the studies, and the likely deviation of the data from a normal distribution, the results in Table 1 are remarkably consistent across studies. Note that the study participants in the study of Andresen *et al.* (56) were younger than those of the other authors. Overall, for an OLVF detection sensitivity of around 78%, for Caucasian women the QCT LS BMD threshold is around 90 mg/mL, while it is around 60 mg/mL for East Asian women. Table 2 further shows that, when the Caucasian women QCT LS BMD threshold is 80 mg/mL, the OLVF detection sensitivity is around 60%, while for East Asian women the corresponding threshold is around 50 mg/mL.

The data in Table 1 and Table 2 are supported by other reports that, for East Asian women, vertebral fragility fractures occur at a lower BMD than is typical for

Caucasian women. For example, Jiang *et al.* (59) described their QCT LS BMD results for postmenopausal women with radiographic OLVF. For a wedge type of OLVF, mean QCT LS BMD was 45.1±23.8 mg/mL (n=36, age: 70.3±8.0 years); while for the biconcave type of OLVF, mean QCT LS BMD was 32.1±24.51 mg/mL (n=40, age: 70.9±7.8 years). In a study of mixed-sex older Chinese patients (>50 years), Xie *et al.* (60) reported that their spine fracture group (n=58) had QCT LS BMDs that ranged from 21 to 65 mg/mL, while the nonfracture group (n=62) had BMD values ranging from 55 to 121 mg/mL. On the other hand, for Caucasian women, spine fractures typically occur at a higher QCT LS BMD (around 70 mg/mL) (25,48,51,53–55,61).

In conclusion, this article provides further evidence that for East Asian women, a QCT LS BMD threshold of 80 mg/mg is too high for classifying osteoporosis (29). While hereby we are not arguing 45–50 mg/mL is the most suitable threshold for classifying osteoporosis in East Asian women, we argue that for East Asian women, the QCT LS BMD value equivalent to the Caucasian women's threshold of 80 mg/mL is about 45–50 mg/mL.

Table 2 Radiographic OLVF detection sensitivity when QCT lumbar spine BMD is <80 mg/mL for Caucasian women and <45–50 mg/mL for East Asian women

Authors	Non-OLVF		OLVF		QCT BMD* (mg/mL)	Sensitivity (%)
	n	Age (years)	n	Age (years)		
Caucasian women data						
Jergas <i>et al.</i> (53)	56	68.0±6.1	55	67.9±6.5	<80.0	52.7
Lang <i>et al.</i> (48)	45	71.5±4.4	26	76.1±6.5	<80.0	65.4
Duboeuf <i>et al.</i> (54)	83	63.6	29	66.6	<80.9	69.0
Cann <i>et al.</i> (55)	20	57.1±10.1	91	62.8±8.0	<80.0	71.4
Andresen <i>et al.</i> (56)		229 women, 17 men, 57.4 (33–87)			<80.6	56.5
East Asian women data						
Ito <i>et al.</i> (25)	118	64.3±2.6	67	64.9±6.9	<50.7	51.5
Youn <i>et al.</i> (38)	290	61.9±6.3	34	70.4±7.1	<51.2	55.9
Lin <i>et al.</i> (17)	296 [†]	65.4±9	205 [‡]	72.5±9.7	<50.1	55.6
Qin <i>et al.</i> (57)	80	50–70	80	50–70	<46.4	70.0
Mao <i>et al.</i> (58)	198	68 (61–75)	198	68 (61–75)	<45.1	66.7

Age data are represented as mean ± standard deviation or mean and range. *, simulated results assuming normal distribution of QCT BMD data; [†], 74.3% female; [‡], 85.4% female. Results of Cann *et al.* were based on Fig. 6 in reference 55 (Cann *et al.*). OLVF, osteoporotic-like vertebral fracture; QCT, quantitative computed tomography; BMD, bone mineral density.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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