JOURNAL OF WOMEN'S HEALTH
Volume 00, Number 00, 2018

DOI: 10.1089/jwh.2018.7310

Bone Mineral Density and Breast Cancer Incidence and Mortality in Postmenopausal Women: A Long-Term Follow-Up Study

Wolfgang Brozek, PhD,[1] Gabriele Nagel, MD,[1,2] Hanno Ulmer, PhD,[1,3] and Hans Concin, MD[1]

Abstract

Purpose: To examine whether bone mineral density (BMD) is predictive of breast cancer risk and mortality in a population of early postmenopausal women participating in a medical prevention program in western Austria.
Patients and Methods: Between May 1991 and February 1999, lumbar spine BMD was measured by dual-energy X-ray absorptiometry ($N = 1163$, mean age 56.9 ± 5.7 years) or quantitative computed tomography ($N = 2283$, mean age 56.8 ± 5.4 years) in 3446 women aged ≥50 years. Data on medication and lifestyle factors were collected by questionnaire. Participants were prospectively followed up for breast cancer incidence, and breast cancer patients were followed up for mortality. To calculate risk of breast cancer and mortality, Cox proportional hazards models were applied.
Results: During median follow-up of 20.7 years, 185 invasive breast cancer cases and 22 deaths due to breast cancer occurred. Risk of breast cancer in the highest versus the lowest BMD quartile was nonsignificantly reduced, in particular when follow-up was restricted to 10 years (hazard ratio 0.53, 95% confidence interval 0.25–1.12). There was no risk reduction when follow-up began 10 years after BMD measurement. There was no association between BMD and all-cause or breast cancer-specific mortality among breast cancer patients, but a trend toward reduced mortality risk in the highest BMD quartile.
Conclusions: We hypothesize that BMD is not reflective of estrogen exposure and not predictive of breast cancer risk, at least in young postmenopausal women. Confounders such as vitamin D might underlie low breast cancer risk at high BMD, thus mirroring better health status.

Keywords: breast cancer, bone mineral density, DXA, QCT, VHM&PP

Introduction

Both breast cancer and osteoporosis are diseases with peak incidence and prevalence after menopause.[1,2] While the incidence of osteoporosis steadily increases with age,[2] the increment in breast cancer incidence, however, markedly slows down after menopause.[1] It has been suggested that estrogen is the underlying key factor that plays important roles in both pathologic conditions. Not only is estrogen involved in regulation of bone metabolism by inhibition of bone resorption[3] but it also promotes breast tumorigenesis[4] *via* estrogen receptor-mediated stimulation of cell proliferation[5] and generation of reactive oxygen species.[6] Therefore, declining postmenopausal levels of estrogen are considered to potentially entail both detrimental and beneficial effects on bone and breast, respectively.

Bone mineral density (BMD) is a parameter of bone quantity that (beside bone quality) contributes toward bone strength based on which osteoporosis is diagnosed.[7] In clinical routine, BMD is not only most commonly assessed using dual-energy X-ray absorptiometry (DXA) but also quantitative computed tomography (QCT) is a widely applied method.[8] BMD has been suggested to reflect lifetime exposure to estrogen that is affected by age of menarche and menopause, the use or lack of use of hormone replacement therapy (HRT) after menopause, and body–mass index (BMI).[9] While a greater length of time between menarche and menopause, the use of HRT, and higher BMI have been associated with elevated risk of breast cancer, the opposite is true for osteoporosis and the risk of osteoporotic fractures.[9,10] Accordingly, higher BMD should mirror longer exposure to estrogen and be a predictor of breast cancer risk.

[1]Agency for Preventive and Social Medicine, Bregenz, Austria.
[2]Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany.
[3]Department of Medical Statistics, Informatics and Health Economics, Innsbruck Medical University, Innsbruck, Austria.

A wealth of studies foremost in postmenopausal women have in fact demonstrated a positive relationship between BMD and breast cancer risk,[11–25] and this has been confirmed by two meta-analyses, one including investigations in postmenopausal women[26] and the other allowing for prospective studies[27] only. In addition, breast cancer recurrence rates were decreased in postmenopausal breast cancer patients with low versus normal BMD.[28] A previous review, however, stated considerable variation in study results and no conclusive evidence for a role of BMD as an indicator for breast cancer risk.[29] Indeed, several investigations that found no association questioned the utility of BMD to predict risk of breast cancer,[27,30–34] and no correlation of mammographic breast density, a surrogate marker for breast cancer risk, with BMD was reported in a recent review.[35] With respect to survival upon breast cancer diagnosis, higher BMD was found to be unfavorable,[17] whereas another study showed no association.[24]

In view of such contradictory epidemiological notions, we followed up a large cohort of postmenopausal women who had BMD measured at the lumbar spine by DXA or QCT within the scope of a preventive medicine program in Austria.[36] The present study is the first to examine BMD-related breast cancer risk based on QCT data. Moreover, women who developed breast cancer were monitored for all-cause and breast cancer-specific mortality.

Patients and Methods

Study design and data acquisition

In the 1990s, more than 5000 women were enrolled in a general preventive medicine activity for peri- and postmenopausal women with additional focus on mental and bone health in Vorarlberg, the westernmost province of Austria,[36] in the overarching context of the Vorarlberg Health Monitoring & Prevention Program (VHM&PP).[37] During this activity, BMD was measured in 4107 participants between May 1991 and February 1999 at the lumbar spine by DXA or QCT (Fig. 1), whichever device was available depending on the residency of participants.

Upon exclusion of prevalent breast cancer cases at the time of BMD measurement, missing or implausibly high or low BMD values, and patients aged <50 years, 3446 women were prospectively followed up for breast cancer incidence and censored by date of death or by December 31, 2015, that is, the last date of the study period for which breast cancer diagnoses were recorded, whichever came first. The mortality registry of the Statistics Austria database[38] informed about date of death due to any cause. Dates of breast cancer diagnosis as well as of death from breast cancer were obtained from the cancer registry of Vorarlberg, identification of cases conformed to the International Classification of Diseases, 9th revision (ICD-9) and International Classification of Diseases, 10th revision (ICD-10) code classes 174 and C50, respectively. The Ethics Committee of Vorarlberg gave its approval for evaluation of the VHM&PP data, and all procedures were in accordance with the Declaration of Helsinki.

Exposure

BMD was recorded from the lumbar spine using DXA or QCT. Quartile cut points were calculated for DXA and QCT results separately. Evaluation of combined results relied upon the calculation of z-scores [$z = (x - \mu)/\sigma$, where x is the actual level of exposure, μ is the mean, and σ the standard deviation] that were calculated for DXA and QCT separately. Quartiles for all results of both DXA and QCT were delimited from z-scores combined from both methods.

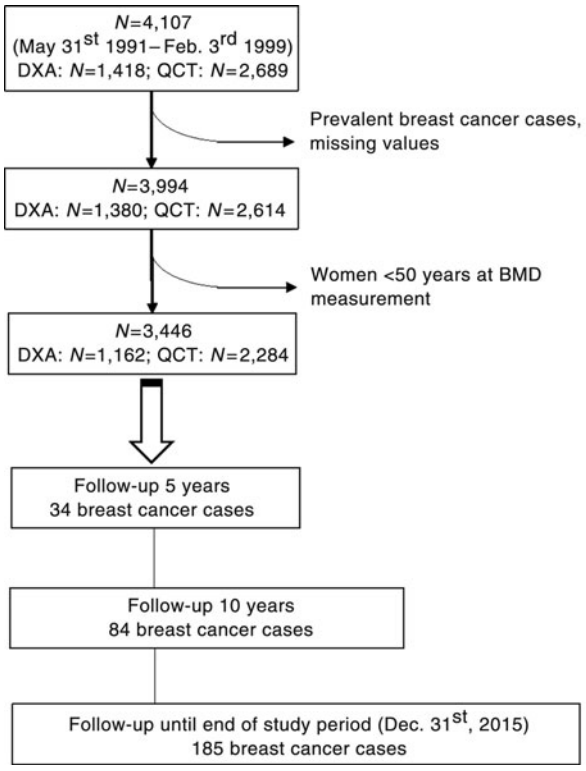

FIG. 1. Flow diagram of the selection of the study population.

Outcomes

Women underwent BMD measurement on the day of recruitment to the study and were followed up for incident breast cancer as a primary outcome. For survival analysis among women with breast cancer diagnosis ($n = 185$), as defined by the ICD-9 and ICD-10 code classes 174 and C50, respectively, end points were both all-cause and breast cancer-specific mortality.

Covariates

For the analysis of incident breast cancer, variables adjusted for included age at BMD measurement and other variables known or suspected to influence breast cancer risk that were acquired using a questionnaire, that is, BMI, smoking status, physical activity, HRT, hysterectomy, and thyroid medication. Menstrual cycle duration was not accounted for because this variable was missing for 521 women (15.1%). Covariates in the analysis of survival from breast cancer included age at breast cancer diagnosis, time from BMD measurement to breast cancer diagnosis, BMI, hysterectomy status, and tumor stage. Information on histological tumor

grading was available only for 135 patients and therefore disregarded.

Statistical analyses

Cox proportional hazards models served to obtain hazard ratios (HRs) for breast cancer incidence and all-cause and breast cancer-specific mortality. The chi-square test was applied for comparison of discrete variables, and Student's *t*-test or Mann–Whitney *U*-test served as parametric versus nonparametric methods, respectively, to compare continuous variables. The Shapiro–Wilk and Kolmogorov–Smirnov tests informed on normality or non-normality of distribution. Applying a confidence level of 95%, differences were considered statistically significant at $p < 0.05$. All analyses were conducted using SPSS, version 19 (SPSS, Inc., Chicago, IL), and Systat, version 13 (Systat Software, Inc., Chicago, IL).

Results

In our study cohort, postmenopausal women presented at mean age of 56.8 ± 5.5 years for BMD measurement (Table 1). During median follow-up of 20.7 years (IQR: 3.8 years; range: 0.1–24.6 years), 185 women were diagnosed with breast cancer, 22 of whom also died of breast cancer. Women who developed breast cancer were younger at the time of BMD measurement (55.9 ± 4.5 years) than those who remained without breast cancer (56.9 ± 5.6 years), but this difference just barely missed statistical significance ($p = 0.05$).

None of the covariates differed statistically significantly between women who developed versus those who did not develop breast cancer. Likewise, the average BMD did not significantly differ between the breast cancer group versus no breast cancer group, both measured by DXA in 1163 individuals (0.93 ± 0.17 g/cm^2 vs. 0.92 ± 0.16 g/cm^2, respectively) and by QCT in 2283 individuals (95.30 ± 24.02 mg/cm^3 vs. 94.69 ± 26.97 mg/cm^3). Cut points for the assignment of BMD values into quartiles were the 25th, 50th, and 75th percentiles: 0.814, 0.916, and 1.026 g/cm^2 for DXA and 76.20, 93.25, and 111.50 mg/cm^3 for QCT.

HRs for breast cancer risk in *z*-score quartiles based on BMD by both DXA and QCT are shown in Table 2. For the complete follow-up time, we observed a conspicuous, but nonsignificant, decline in breast cancer risk in the fourth quartile representing the highest BMD values, both in the age-adjusted and fully adjusted models (HR 0.76, 95% confidence interval [CI] 0.47–1.21, for both models). Confining

Table 1. Baseline Characteristics of the Study Population

	All subjects (n = *3446*)	*No breast cancer* (n = *3261*)	*Breast cancer* (n = *185*)	p
Age at recruitment, years, mean ± SD	56.8 ± 5.5	56.9 ± 5.6	55.9 ± 4.5	0.05
BMI, kg/m^2, mean ± SD	25.4 ± 3.9	25.4 ± 3.9	25.7 ± 3.9	0.36
BMI, kg/m^2, *n* (%)				0.87
<25	1789 (52.3)	1695 (52.3)	94 (50.8)	
25–30	1209 (35.3)	1143 (35.3)	66 (35.7)	
>30	425 (12.4)	400 (12.4)	25 (13.5)	
Smoking status, *n* (%)				0.76
Never	2588 (75.1)	2453 (75.2)	135 (73.0)	
Former	482 (14.0)	453 (13.9)	29 (15.7)	
Current	375 (10.9)	354 (10.9)	21 (11.3)	
Physical activity/sports, *n* (%)				0.45
None	1785 (51.8)	1688 (51.7)	97 (52.4)	
Up to 1 hour/week	696 (20.2)	652 (20.0)	44 (23.8)	
1–2 hours/week	432 (12.5)	410 (12.6)	22 (11.9)	
>2 hours/week	533 (15.5)	511 (15.7)	22 (11.9)	
Menstrual cycle duration, years, *n* (%)				0.70
<30	702 (24.0)	663 (24.0)	39 (24.7)	
30–40	2008 (68.6)	1902 (68.7)	106 (67.1)	
>40	215 (7.4)	202 (7.3)	13 (8.2)	
HRT, *n* (%)				0.34
No	2669 (77.5)	2531 (77.6)	138 (74.6)	
Yes	777 (22.5)	730 (22.4)	47 (25.4)	
Hysterectomy, *n* (%)				0.75
No	2423 (70.3)	2291 (70.3)	132 (71.4)	
Yes	1023 (29.7)	970 (29.7)	53 (28.6)	
Thyroid medication, *n* (%)				0.12
No	3175 (92.1)	2999 (92.0)	176 (95.1)	
Yes	271 (7.9)	262 (8.0)	9 (4.9)	
DXA, g/cm^2	0.93 ± 0.16	0.92 ± 0.16	0.93 ± 0.17	0.65
N	1163	1107	56	
QCT, g/cm^3	94.72 ± 26.81	94.69 ± 26.97	95.30 ± 24.02	0.95
N	2283	2154	129	

BMI, body–mass index; DXA, dual-energy X-ray absorptiometry; HRT, hormone replacement therapy; QCT, quantitative computed tomography; SD, standard deviation.

TABLE 2. BREAST CANCER RISK ACCORDING TO *Z*-SCORE QUARTILES OF BONE MINERAL DENSITY AT THE LUMBAR SPINE, RESULTS OF DUAL-ENERGY X-RAY ABSORPTIOMETRY AND QUANTITATIVE COMPUTED TOMOGRAPHY COMBINED, FOR DIFFERENT PERIODS OF FOLLOW-UP

	Full follow-up			*Follow-up up to 10 years*			*Follow-up begun 10 years after BMD*[a]		
		Model			*Model*			*Model*	
	Cases, n	*Adj. for age*[b] *HR (95% CI)*	*Fully adj.*[c] *HR (95% CI)*	*Cases,* n	*Adj. for age*[b] *HR (95% CI)*	*Fully adj.*[c] *HR (95% CI)*	*Cases,* n	*Adj. for age*[b] *HR (95% CI)*	*Fully adj.*[c] *HR (95% CI)*
First quartile	41	1 (ref.)	1 (ref.)	19	1 (ref.)	1 (ref.)	22	1 (ref.)	1 (ref.)
Second quartile	49	1.06 (0.69–1.62)	1.07 (0.70–1.64)	21	0.97 (0.51–1.82)	0.99 (0.52–1.87)	28	1.14 (0.64–2.01)	1.14 (0.64–2.02)
Third quartile	56	1.16 (0.76–1.77)	1.18 (0.77–1.80)	31	1.34 (0.73–2.45)	1.38 (0.75–2.52)	25	0.99 (0.54–1.80)	0.99 (0.54–1.81)
Fourth quartile	39	0.76 (0.47–1.21)	0.76 (0.47–1.21)	13	0.53 (0.25–1.12)	0.54 (0.26–1.15)	26	0.97 (0.52–1.78)	0.94 (0.51–1.74)

[a]Breast cancer cases and censored cases within 10 years after BMD measurement were disregarded in this analysis.
[b]Adjusted for age at recruitment.
[c]Adjusted for age at recruitment, BMI, smoking status, physical activity, HRT, hysterectomy status, and thyroid medication.
BMD, bone mineral density; CI, confidence interval; HR, hazard ratio.

follow-up time to ≤5 years yielded nonsignificantly reduced HRs in the second and fourth quartiles (not shown).

For a follow-up period of ≤10 years, there was an overall statistical significance for all quartiles both in the age-adjusted and the fully adjusted regression models ($p < 0.05$), and HRs slightly rose in the third, but markedly dropped in the fourth quartile, with a near-significant difference of the fourth compared with the first quartile (HR 0.53, 95% CI 0.25–1.12, $p = 0.09$, in the age-adjusted model and HR 0.54, 95% CI 0.26–1.15, $p = 0.11$, in the fully adjusted regression model). By contrast, follow-up disregarding the first 10 years, hence starting 10 years after BMD measurement, entailed no noteworthy variation in breast cancer risk relative to the first BMD quartile.

Separate results for QCT and DXA are shown in Supplementary Tables S1 and S2 (Supplementary Data are available online at www.liebertpub.com/jwh), respectively. None of the HRs differed statistically significantly from breast cancer risk in the first BMD quartile. Results by QCT (Supplementary Table S1) indicated lower risk in the fourth quartile relative to the first quartile for all considered periods of follow-up. Risk in the third quartile was elevated until 10 years of follow-up, but reduced when follow-up began 10 years after BMD measurement. Results by DXA (Supplementary Table S2) showed no remarkable variation of HRs across BMD quartiles for the entire follow-up. However, while HRs relative to the first quartile were reduced for follow-up ≤10 years, they were elevated when follow-up began 10 years after BMD measurement.

We finally conducted a survival analysis among the 185 identified breast cancer cases. Among these, during a median follow-up time of 9.7 years (IQR: 9.7), 37 deaths occurred, 22 of which were due to breast cancer (Table 3). Patients in the fourth BMD quartile exhibited the lowest risk, both when all-cause mortality and breast cancer-specific mortality were the end points, although HRs did not reach the level of statistical significance.

Discussion

The present investigation examined the association between BMD measured at the lumbar spine in early postmenopausal women aged ≥50 years and future incidence of breast cancer as well as survival from breast cancer. Our study is characterized by a long median follow-up time of almost 21 years, surpassed only by an investigation by Zhang et al.[12] where the observation time was 22.1 median years. Furthermore, we analyzed different periods of follow-up, and for the first time, the association of BMD with future breast cancer risk based, in part, on QCT data was examined. Another hallmark of our work is that women entered the study in the context of a medical prevention activity and were therefore presumably relatively healthy.

Our key results suggest that women in the highest in relation to the lowest BMD quartile are at low risk to develop breast cancer. This contrasts with many findings of previous studies cited in the Introduction section. It is notable that women in investigations that did find a positive correlation between BMD and breast cancer risk were (in part considerably) older than in our study, and participants of many of the studies were recruited from osteoporosis trials such as SOF (Study of Osteoporotic Fractures),[11,15] DOES (Dubbo

Table 3. All-Cause and Breast Cancer-Specific Mortality Among 185 Breast Cancer Patients in Quartiles of Bone Mineral Density at the Lumbar Spine, Results of Dual-Energy X-Ray Absorptiometry and Quantitative Computed Tomography Combined

	All-cause mortality			*Breast cancer-specific mortality*		
		Basic[a]	*Fully adj.*[b]		*Basic*[a]	*Fully adj.*[b]
		Model			*Model*	
	Deaths/ survivors, n/n	*HR (95% CI)*	*HR (95% CI)*	*Deaths/ survivors,*[c] n/n	*HR (95% CI)*	*HR (95% CI)*
First quartile	9/32	1 (ref.)	1 (ref.)	4/37	1 (ref.)	1 (ref.)
Second quartile	12/37	1.47 (0.56–3.83)	1.12 (0.40–3.10)	8/41	1.49 (0.42–5.23)	1.14 (0.30–4.36)
Third quartile	10/46	1.03 (0.37–2.82)	0.98 (0.35–2.73)	8/48	1.22 (0.34–4.41)	1.15 (0.31–4.24)
Fourth quartile	6/33	0.81 (0.25–2.62)	0.88 (0.24–3.26)	2/37	0.39 (0.06–2.33)	0.26 (0.02–2.91)

[a]Adjusted for age at breast cancer diagnosis and time from BMD measurement to breast cancer diagnosis.
[b]Adjusted for age at breast cancer diagnosis, time from BMD measurement to breast cancer diagnosis, BMI, hysterectomy status, and tumor stage.
[c]Or death due to causes other than breast cancer.

Osteoporosis Epidemiology Study),[13] EPIDOS (Epidémiologie de l'ostéoporose),[17] FIT (Fracture Intervention Trial),[14] and MORE and CORE trials.[18,20]

On the other hand, studies that failed to detect an association between BMD and breast cancer risk include the report of a population screening program for osteoporosis, where women were well below 50 years when they were DXA scanned,[32] and a cohort study on perimenopausal and early postmenopausal women at a mean age of roughly 53 years.[34] It is therefore conceivable that BMD becomes predictive for breast cancer only after some time of estrogen cessation, especially when cancers develop at a later age.

Herein, the reason why we found even reduced HRs in the highest BMD quartile relative to the lowest (on the verge of statistical significance) can only be hypothesized. Since women in our study were participants of a medical prevention program, one can assume that they were adopting an above average health conscious attitude and leading an above average healthy lifestyle. It is hence feasible that higher BMD is a marker of better health in our study population.

Even though BMD of the lumbar spine is known to be more sensitive to changes in estrogen levels than, for example, BMD of the femoral neck,[39] lumbar spine BMD was not associated with significantly increased breast cancer risk in some studies that found a correlation at other skeletal sites. For example, Cauley et al.[18] observed an association with breast cancer risk at the femoral neck only, and Fraenkel et al.[24] reported significantly increased HRs for the highest tertile of BMD z-scores at the femoral neck and total hip, but not the lumbar spine. In addition, the bulk of those investigations that did not find a correlation of BMD with breast cancer risk included lumbar spine BMD.[31–34]

This is a strong indication in favor of a nonexclusive role of estrogen in dictating the risk for breast cancer, thus confounding factors might obscure or even revert the association between estrogen and breast cancer risk. For example, vitamin D and calcium, while exerting beneficial effects on BMD, play important roles in the prevention of chronic diseases and cancer, particularly breast cancer.[40] Furthermore, proinflammatory cytokines such as IL-1β, IL-6, and TNF-α released during estrogen withdrawal, in chronic inflammatory conditions, and by (still undetected) tumors are promoters of tumor progression, while negatively impinging upon BMD.[41]

Interestingly, women with breast cancer have been shown to be at higher risk for osteoporotic fractures than women without breast cancer, independent of chemotherapy or aromatase inhibitors and independent of BMD.[42] This implies that inherent factors such as released by the tumor negatively affect bone quality rather than quantity, which is not captured by BMD. This further highlights the complex interaction between bone and tumor biology, which cannot be reduced to one single factor, that is, estrogen.

Apart from combined results for BMD measured by DXA and QCT, we herein also present separate results for each of the methods, although numbers are small especially for data obtained by DXA. Even though neither method was associated with a statistically significant increase of breast cancer risk in the highest versus the lowest quartile of BMD, we also observed differences. The decline in breast cancer risk in the fourth quartile was carried by QCT rather than DXA data. Moreover, while HRs for follow-up $\leq$10 years in the third BMD quartile increased according to QCT, we observed a decrease by DXA. In addition, for follow-up starting 10 years after BMD measurement, HRs in relation to the lowest quartile were (nonsignificantly) elevated only by DXA.

Such disparate trends could be due to the different methodologies utilized by QCT and DXA. Whereas QCT performs a volumetric analysis of the trabecular BMD of the spine, DXA yields the average BMD of both the cortical and the trabecular zones.[43] It is known that owing to its higher metabolic activity compared with cortical bone, trabecular bone is more sensitive to physiological alterations such as hormonal changes. Therefore, declining estrogen levels in postmenopausal women should be more appropriately reflected by BMD measured by QCT, whereas BMD measured by DXA should be more suitable to assess long-term exposure to estrogen. Both aspects might play a role for evaluation of breast cancer risk. However, with respect to the relatively small numbers in the DXA analysis, any differences in our results obtained by QCT and DXA should be interpreted cautiously.

In addition, risk factors for breast cancer might not remain the same after recruitment to the study and may change over

time, which could explain the different risk profiles over BMD quartiles whether follow-up ended or began 10 years after BMD measurement.

It remains to be explored whether our results justify a recommendation for delayed mammography based on lumbar spine BMD in early postmenopausal populations. Results from older populations are conflicting. In one study, continuing mammography screening beyond the age of 69 was found to be cost-effective for the highest BMD quartiles when BMD was measured at the age of 65,[44] whereas Kritz-Silverstein et al.[33] concluded that BMD measured beyond the age of 65 years had no predictive value for breast cancer and should not be used as a criterion for mammography. In view of such ambiguous findings and the presumable good health status of our study participants, more data from further studies on lumbar spine BMD based on QCT and its association with breast cancer risk are needed.

Our results of the survival analysis among women who developed breast cancer followed the same trend as the incidence insofar as the highest quartile was (nonsignificantly) associated with the lowest hazards of death, both for all-cause and breast cancer-specific mortality. This finding is also in agreement with the conjecture that women with the highest BMD are the healthiest ones in our study population. Moreover, the fact that (of 185 breast cancer cases) there were only 37 deaths due to all causes and 21 breast cancer-related deaths during a very long follow-up time underscores the high standard of health surveillance and disease prevention in Vorarlberg and the high degree of health awareness among the population, not least by virtue of activities offered by the VHM&PP.[37]

Two other studies have explored BMD-related survival among breast cancer patients. Ganry et al.[17] found significantly elevated all-cause mortality in the middle and highest BMD tertiles relative to the lowest for BMD measured at three skeletal sites, that is, the trochanter, Ward's triangle, and femoral neck, in a very old (≥75 years) osteopenic and osteoporotic study population. By contrast, in a distinctly younger population, 5-year survival was not dependent upon tertiles of BMD *z*-scores of the femoral neck, even though breast cancer incidence was increased in the highest BMD tertile of the same site.[24] Even considering that time of BMD measurement and time of breast cancer diagnosis could be far apart and risk factors might thus change, our results are in line with the finding that risk for mortality is not increased in an early postmenopausal study population.

There are not only a number of limitations but also strengths that characterize the present investigation. First, since women in our study were recruited during a voluntary medical prevention program that was free of cost for participants, it can be assumed that our study population was relatively healthy, according to the healthy volunteer effect.[45] However, owing to a long-standing tradition of disease prevention and health awareness in Vorarlberg,[37] it might be that results of the study are indeed representative of the whole population of the same age.

Next, average age at recruitment was early after menopause, so our results are arguably not applicable to older predominantly osteoporotic populations. On the other hand, findings from studies on osteoporotic populations should not be compatible with reports on premenopausal and early postmenopausal women such as in our study.

In addition, no information was available on vitamin D status and alcohol consumption, both factors that interfere with bone and cancer metabolism. Neither was prescription of HRT following BMD measurement known. However, since the use of hormones was at best moderate in Austria and other European countries[46] in the 1990s and HRT before 60 years of age or within 10 years after menopause is regarded to be safe with respect to breast cancer risk,[47,48] we suspect HRT is not a relevant confounder in our population of relatively young postmenopausal women.

Moreover, several factors affecting foremost survival were not accounted for in our study. These include histological tumor grading that was known only for a proportion of patients and hormone receptor and HER2 statuses that were not available in our database. Likewise, we had no information on family history of breast cancer, which could have conferred increased risk of both incidence and mortality, and cancer therapy. Strengths of our study, on the other hand, include the long follow-up time that permitted analysis of distinct subperiods and the possibility to assess breast cancer risk based on two methods for BMD measurement, that is, DXA and QCT, the latter of which was used for the first time for this purpose.

Conclusions

We have found that in a population of early postmenopausal women, BMD of the lumbar spine measured by two techniques was not positively correlated with risk of breast cancer, which agrees with other studies in pre- and early postmenopausal women. Even though our findings are not to be regarded as definitive evidence, they give rise to the hypothesis that BMD is not reflective of estrogen exposure and therefore not predictive of breast cancer risk. Neither was BMD predictive of breast cancer patients' survival in our study population. In contrast to other investigations, however, we observed a slight protective effect of the highest BMD on development of breast cancer, which might reflect an association between good bone health and good general health status that could tentatively be related to vitamin D or other confounders.

Acknowledgments

The authors thank Elmar Stimpfl and Karin Parschalk from the aks gesundheit for excellent technical support, Christian Bernhard and Gabriela Dür from the Vorarlberg State Government, and finally, all the study participants.

Author Disclosure Statement

No competing financial interests exist.

References

1. McPherson K, Steel CM, Dixon JM. ABC of breast diseases. Breast cancer-epidemiology, risk factors, and genetics. BMJ 2000;321:624–628.
2. Hernlund E, Svedbom A, Ivergård M, et al. Osteoporosis in the European Union: Medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 2013;8:136.

3. Khosla S, Oursler MJ, Monroe DG. Estrogen and the skeleton. Trends Endocrinol Metab 2012;23:576–581.
4. Vorherr H. Endocrinology of breast cancer. Maturitas 1987; 9:113–122.
5. Singh RR, Kumar R. Steroid hormone receptor signaling in tumorigenesis. J Cell Biochem 2005;96:490–505.
6. Wen C, Wu L, Fu L, Wang B, Zhou H. Unifying mechanism in the initiation of breast cancer by metabolism of estrogen (Review). Mol Med Rep 2017;16:1001–1006.
7. Cefalu CA. Is bone mineral density predictive of fracture risk reduction? Curr Med Res Opin 2004;20:341–349.
8. Oei L, Koromani F, Rivadeneira F, Zillikens MC, Oei EHG. Quantitative imaging methods in osteoporosis. Quant Imaging Med Surg 2016;6:680–698.
9. Tremollieres F, Ribot C. Bone mineral density and prediction of non-osteoporotic disease. Maturitas 2010;65: 348–351.
10. Dall GV, Britt KL. Estrogen effects on the mammary gland in early and late life and breast cancer risk. Front Oncol 2017;7:110.
11. Cauley JA, Lucas FL, Kuller LH, Vogt MT, Browner WS, Cummings SR. Bone mineral density and risk of breast cancer in older women: The study of osteoporotic fractures. JAMA 1996;276:1404–1408.
12. Zhang Y, Kiel DP, Kreger BE, et al. Bone mass and the risk of breast cancer among postmenopausal women. N Engl J Med 1997;336:611–617.
13. Nguyen TV, Center JR, Eisman JA. Association between breast cancer and bone mineral density: The Dubbo Osteoporosis Epidemiology Study. Maturitas 2000;36: 27–34.
14. Buist DSM, LaCroix AZ, Barlow WE, White E, Weiss NS. Bone mineral density and breast cancer risk in postmenopausal women. J Clin Epidemiol 2001;54:417–422.
15. Zmuda JM, Cauley JA, Ljung B-M, Bauer DC, Cummings SR, Kuller LH. Bone mass and breast cancer risk in older women: Differences by stage of diagnosis. J Natl Cancer Inst 2001;93:930–936.
16. van der Klift M, de Laet CEDH, Coebergh JWW, Hofman A, Pols HAP. Bone mineral density and the risk of breast cancer: The Rotterdam Study. Bone 2003;32:211–216.
17. Ganry O, Baudoin C, Fardellone P, Peng J, Raverdy N. Bone mass density and risk of breast cancer and survival in older women. Eur J Epidemiol 2004;19:785–792.
18. Cauley JA, Song J, Dowsett SA, Mershon JL, Cummings SR. Risk factors for breast cancer in older women: The relative contribution of bone mineral density and other established risk factors. Breast Cancer Res Treat 2007;102: 181–188.
19. Hadji P, Gottschalk M, Ziller V, Kalder M, Jackisch C, Wagner U. Bone mass and the risk of breast cancer: The influence of cumulative exposure to oestrogen and reproductive correlates. Results of the Marburg breast cancer and osteoporosis trial (MABOT). Maturitas 2007;56:312–321.
20. Burshell AL, Song J, Dowsett SA, et al. Relationship between bone mass, invasive breast cancer incidence and raloxifene therapy in postmenopausal women with low bone mass or osteoporosis. Curr Med Res Opin 2008;24: 807–813.
21. Chen Z, Arendell L, Aickin M, Cauley J, Lewis CE, Chlebowski R. Hip bone density predicts breast cancer risk independently of Gail score: Results from the Women's Health Initiative. Cancer 2008;113:907–915.
22. Grenier D, Cooke AL, Lix L, Metge C, Lu H, Leslie WD. Bone mineral density and risk of postmenopausal breast cancer. Breast Cancer Res Treat 2011;126: 679–686.
23. Kalder M, Jäger C, Seker-Pektas B, Dinas K, Kyvernitakis I, Hadji P. Breast cancer and bone mineral density: The Marburg Breast Cancer and Osteoporosis Trial (MABOT II). Climacteric 2011;14:352–361.
24. Fraenkel M, Novack V, Liel Y, et al. Association between bone mineral density and incidence of breast cancer. PLoS One 2013;8:e70980.
25. Kim B-K, Choi Y-H, Song Y-M, et al. Bone mineral density and the risk of breast cancer: A case-control study of Korean women. Ann Epidemiol 2014;24:222–227.
26. Qu X, Zhang X, Qin A, et al. Bone mineral density and risk of breast cancer in postmenopausal women. Breast Cancer Res Treat 2013;138:261–271.
27. Nagel G, Peter RS, Klotz E, Brozek W, Concin H. Bone mineral density and breast cancer risk: Results from the Vorarlberg Health Monitoring & Prevention Program and meta-analysis. Bone Rep 2017;7:83–89.
28. Zambetti A, Tartter PI. Bone mineral density is a prognostic factor for postmenopausal Caucasian women with breast cancer. Breast J 2013;19:168–172.
29. Zain NM, Seriramulu VP, Chelliah KK. Bone mineral density and breast cancer risk factors among premenopausal and postmenopausal women—A systematic review. Asian Pac J Cancer Prev 2016;17:3229–3234.
30. Buist D, LaCroix AZ, Barlow WE, et al. Bone mineral density and endogenous hormones and risk of breast cancer in postmenopausal women (United States). Cancer Causes Control 2001;12:213–222.
31. Kerlikowske K, Shepherd J, Creasman J, Tice JA, Ziv E, Cummings SR. Are breast density and bone mineral density independent risk factors for breast cancer? J Natl Cancer Inst 2005;97:368–374.
32. Stewart A, Kumar V, Torgerson DJ, Fraser WD, Gilbert FJ, Reid DM. Axial BMD, change in BMD and bone turnover do not predict breast cancer incidence in early postmenopausal women. Osteoporos Int 2005;16:1627–1632.
33. Kritz-Silverstein D, Schneider DL, Sandwell J. Breast cancer and bone mass in older women: Is bone density prescreening for mammography useful? Osteoporos Int 2006;17:1196–1201.
34. Trémollieres FA, Pouillès J-M, Laparra J, Ribot C. Bone mineral density at menopause does not predict breast cancer incidence. Osteoporos Int 2008;19:1497–1504.
35. Lee JM, Holley S, Appleton C, Toriola AT. Is there an association between bone mineral density and mammographic density? A systematic review. J Womens Health (Larchmt) 2017;26:389–395.
36. Concin H, Ulmer H, Hefler L. Mental well-being in 5000 women participating in the 'Women-Plus' preventive medicine program. Maturitas 2002;41:S9–S12.
37. Concin H, Nagel G, Ulmer H, eds. Modern Prevention Research in Vorarlberg. 50 Years of Preventive Medicine and Research in the Agency for Preventive and Social Medicine. Bregenz: aks Gesundheit GmbH, 2013.
38. Statistik Austria. http://www.statistik.at. Accessed May 15, 2018.
39. Cauley JA. Estrogen and bone health in men and women. Steroids 2015;99:11–15.

40. Peterlik M, Boonen S, Cross HS, Lamberg-Allardt C. Vitamin D and calcium insufficiency-related chronic diseases: An emerging world-wide public health problem. Int J Environ Res Public Health 2009;6:2585–2607.
41. Mundy GR. Osteoporosis and inflammation. Nutr Rev 2007;65(Suppl 3):S147–S151.
42. Fraenkel M, Geffen DB, Novack V, et al. Breast cancer survivors are at an increased risk for osteoporotic fractures not explained by lower BMD: A retrospective analysis. NPJ Breast Cancer 2015;1:15010.
43. Adams JE. Quantitative computed tomography. Eur J Radiol 2009;71:415–424.
44. Kerlikowske K, Salzmann P, Phillips KA, Cauley JA, Cummings SR. Continuing screening mammography in women aged 70–79 years: Impact on life expectancy and costeffectiveness. JAMA 1999;282:2156–2163.
45. Froom P, Melamed S, Kristal-Boneh E, Benbassat J, Ribak J. Healthy volunteer effect in industrial workers. J Clin Epidemiol 1999;52:731–735.
46. Schneider HP. Cross-national study of women's use of hormone replacement therapy (HRT) in Europe. Int J Fertil Womens Med 1997;42(Suppl 2):365–375.
47. de Villiers TJ, Gass MLS, Haines CJ, et al. Global Consensus Statement on menopausal hormone therapy. Climacteric 2013;16:203–204.
48. de Villiers TJ, Pines A, Panay N, et al. Updated 2013 International Menopause Society recommendations on menopausal hormone therapy and preventive strategies for midlife health. Climacteric 2013;16:316–337.

Address correspondence to:
Wolfgang Brozek, PhD
Agency for Preventive and Social Medicine
Rheinstr. 61
Bregenz 6900
Austria

E-mail: wolfgang.brozek@aks.or.at