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Bone mineral density and breast cancer risk: Results from the Vorarlberg Health Monitoring & Prevention Program and meta-analysis

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ABSTRACT

We investigated the association between bone mineral density (BMD) and breast cancer risk in a large prospective cohort and quantified the evidence in a meta-analysis of prospective studies.

Baseline BMD has been measured by dual energy X-ray absorptiometry (DXA, N = 1418). Data on medication and lifestyle has been collected by questionnaire. Cox proportional Hazards models were applied to calculate Hazard Ratios for breast cancer. In addition, a meta-analysis on categorical and dose-response values including the current results has been performed applying random-effects models.

During mean follow-up of 16.3 (SD 3.3) years of 1380 women (mean age 55.5 ± 6.3 years), 52 cases of invasive breast cancer were identified. We found no statistically significant association of BMD with breast cancer risk (per one z-score increase, HR 0.91, 95% CI 0.67–1.23).

In the meta-analysis, however, breast cancer risk increased by 15% and 16% per 0.1 g/m^2 increase in BMD at the lumbar spine (95% CI 0.99–1.33) and at the femoral neck (95% CI 1.02–1.32), respectively. Compared to the lowest, the HRs for breast cancer were statistically significant for the highest BMD category, i.e. 1.49 (95% CI 1.04–2.13) at the lumbar spine and 1.66 (95% CI 1.26–2.18) at the femur.

We found no association between BMD (DXA) and breast cancer risk in our cohort. However, overall the present meta-analysis extends and confirms the statistically significant association between increasing BMD and increased breast cancer risk.

1. Introduction

Incidence rates of both osteoporosis and breast cancer increase with age. Just like osteoporosis (Hernlund et al., 2013; Harvey et al., 2010), breast cancer is a major public health problem, with incidence rates expected to rise over the next years (Arnold et al., 2015). Several risk factors for breast cancer have been identified many of which (e.g. early menarche, late menopause, breast feeding and hormone replacement therapy) are related to prolonged estrogen exposure (Howell et al., 2014). The physiological action of estrogen may link breast and bone pathologies (Howell et al., 2014; Khosla, 2010). Since estrogen regulates bone turnover, high bone mineral density (BMD) may be regarded as marker for prolonged cumulative estrogen exposure (Santen et al., 2015).

Measurement of BMD is utilized to assess the osteoporotic status of bone for the prevention of osteoporotic fractures, for which the standard method is dual-energy X-ray absorptiometry (DXA) of the lumbar spine, femoral neck or total hip. BMD could reflect long-term exposure to estrogens and hence serve as intermediate marker of breast cancer risk.

Because estrogen affects both BMD and breast cancer risk, it has been hypothesized that women with high BMD are at increased risk to develop breast cancer. Other potential mechanisms could be related to physical activity and vitamin D intake and activation. There is indeed evidence from a previous meta-analysis that BMD and breast cancer risk are positively correlated (Qu et al., 2013). However, results therein are based on reports varying in study designs, age groups, as well as measurement methods and sites. Moreover, most of these studies were performed among women over 60 years with DXA measurements of the hip (Cauley et al., 1996; Nguyen et al., 2000; Ganry et al., 2004; Kerlikowske et al., 2005; Chen et al., 2008). Considering the long latency time for developing breast cancer, however, measurements at

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younger age with longer follow-up may be more appropriate.

The aims of our study were to investigate the association between BMD and breast cancer risk among women in a large prospective cohort study with long-term follow-up and to quantify the evidence of a relationship between BMD and breast cancer risk in a meta-analysis including prospective studies.

2. Patients and methods

2.1. Participants

Within the framework of the Vorarlberg Health Monitoring & Prevention Program (VHM & PP), 4550 women were recruited between July 1991 and May 1999 for a prevention activity especially tailored for women with climacteric complaints, i.e. "Women-50plus" that has been described in detail before (Concin et al., 2002). In brief, data on physical and mental well-being, medication, physical activity and smoking status were collected by questionnaire, and height, weight and blood pressure were measured. Ethical approval for the evaluation of the VHM & PP data was obtained by the ethics committee of Vorarlberg. In order to identify women with osteoporosis, bone mineral density was measured at recruitment. Baseline BMD of 4107 women has been measured by dual energy X-ray absorptiometry (DXA, N = 1418) or quantitative computer tomography (QCT, N = 2689) depending on the place of residence.

2.2. Exposure

Overall, 1418 women underwent DXA scanning at the lumbar spine at baseline. After exclusion of prevalent breast cancer cases and data due to missing and implausible values, BMD data of 1380 women were available for the analyses.

Quartile cut-points were defined for DXA. In addition, we transformed the original values to standardized variables (z-scores) with zero as mean and one as standard deviation. Hence the z-score was calculated as: $z = (x - \mu)/\sigma$, where μ is the mean, σ is the standard deviation, and x is the actual level of the exposure.

2.3. Outcome

Incident breast cancer cases were identified in the Vorarlberg cancer registry in accordance with the code C50 of the International Classification of Diseases, 10th revision (ICD-10). Data on vital status were obtained from the mortality registry at Statistics Austria. Person-years under observation for each woman were calculated until the date of cancer diagnosis or the date of death, whichever came first. Participants were censored by December 31, 2011.

2.4. Covariates

Adjustment has been performed for body mass index (BMI, kg/m^2), smoking status (smoker, ex-smoker, non-smoker), hormone replacement therapy (HRT) use (yes, no), menstrual cycle duration (menses, < 30, 30–40, > 40 years), hysterectomy (yes, no), menopausal status (< 50, ≥ 50 years), use of thyroid medication (yes, no), and leisure time physical activity (none, 30 min, 30–60 min, 60–120 min, > 120 min/week).

2.5. Statistical analysis

A cohort study design was used in order to investigate the association between DXA and breast cancer risk. Bivariate comparisons of women who developed breast cancer and those who did not were performed using *t*-test for continuous variables and χ^2-test for categorical variables. Cox proportional hazards models were fitted to obtain Hazard Ratios (HRs) with 95% confidence intervals (CIs) for breast cancer. The models were adjusted for age at recruitment (years) and smoking status (four categories: never, former, current smokers and unknown). Additional models were calculated adjusting for BMI, menstrual cycle duration, HRT use, leisure time physical activity and thyroid medication.

2.6. Meta-analysis

A systematic literature research limited to publications in English, has been carried out using Medline PubMed (1980 till December 31, 2014) using abstracts, titles and MeSH headings. For the exposure we searched the terms "bone mineral density", "bone density", "BMD" and for the outcome "breast cancer", "breast tumor" and "Breast Neoplas*". PubMed search term: bone mineral density[Title/Abstract] OR bone density[Title/Abstract] OR BMD[Title/Abstract] OR Bone Density [MH]) AND (breast cancer[Title/Abstract] OR breast tumor[Title/Abstract] OR Breast Neoplas* OR Breast Neoplasms[MH]) AND English [Language] AND ("1980/01/01"[PDAT]: "2014/12/31"[PDAT]). In addition, the references lists were screened for relevant publications.

Two reviewers evaluated the studies with respect to the inclusion criteria and the predefined quality indicators. Inclusion criteria were: 1) cohort or case-control study, 2) BMD as exposure variable, 3) breast cancer as outcome variable, and 4) the report of a relative risk estimate. In case of discrepancies, a consensus was reached by discussion. Studies in which other methods than DXA were applied were not included in the meta-analysis. Furthermore, a standardized reporting form was used to collect the following relevant data: first author's name, publication year, location of the study, study design, menopausal status, BMD assessment, BMD measurement site, sample size, number of breast cancer cases, relative risk estimates and confidence limits, units of measurements and analysis, and comments. Categorical and dose-response meta-analyses were conducted using random-effects models. We did not distinguish between different types of relative risk estimates (risk, rate or odds ratio) based on the assumption that breast cancer is sufficiently rare. Summary relative risks (RRs) were used as common measure of association. The maximally adjusted risk estimates were used for the meta-analysis. For categorical meta-analyses, RRs for the highest versus lowest BMD category were used. For the dose response meta-analyses, estimates for continuous associations were transformed to represent the RR associated with a 0.1 g/m^2 increase in BMD.

To assess heterogeneity, the Cochran Q-test and I^2 statistics were applied. The inverse of the variance of estimates was used as weight and the restricted maximum likelihood estimator was used to quantify heterogeneity. The I^2-values at 25%, 50%, and 75% served as cut-points to define low, moderate and substantial heterogeneity, respectively (Higgins et al., 2003). Funnel plots were displayed to explore publication bias (see Supplemental Figure).

P-values < 0.05 were considered statistically significant. Calculations were carried out with SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). All meta-analyses were conducted using R (R Foundation for Statistical Computing, Vienna, Austria), version 3.0.1.

3. Results

During mean follow-up of 16.3 (SD 3.3) years, 52 cases of invasive breast cancer were identified in 1380 women (Table 1). At baseline, mean age was 55 (SD 6.3) years and mean BMI was 25.2 (SD 3.9) kg/m^2. Of the participants, 27.5% were ever smokers, 21.4% reported HRT use, and 16.8% reported to perform more than two hours of sports per week. The overall mean of DXA results was 0.94 (SD 0.16) g/cm^2, with no statistically significant difference for women who developed breast cancer (0.92 g/cm^2). Concerning the covariates, no statistically significant differences were observed.

Table 2 shows the associations between quartiles of bone mineral density and breast cancer risk. Compared with the lowest quartile of DXA results, HRs for breast cancer risk were statistically non-

Table 1
Baseline characteristics of the study population.

	All subjects	No breast cancer	Breast cancer	P-value
	n = 1380	n = 1328	n = 52	
Age (years), mean (SD)	55.45 (6.3)	55.5 (6.3)	55.1 (5.3)	0.677
BMI (kg/m^2),mean (SD)	25.2 (3.9)	25.2 (4.0)	24.9 (3.7)	0.547
DXA, lumbar spine (g/cm^2), mean (SD)	0.94 (0.16)	0.94 (0.16)	0.92 (0.19)	0.559
Leisure time physical activity (sports), N (%)				0.399
Max. 30 min	731 (53.0)	699 (52.6)	32 (61.5)	
½ h–2 h	417 (30.2)	403 (30.4)	14 (26.9)	
> 2 h	232 (16.8)	226 (17.0)	6 (11.5)	
Smoking status, N (%)				0.927
Never	1000 (72.5)	962 (72.5)	38(73.1)	
Ever	379 (27.5)	365 (27.5)	14 (26.9)	
Menstrual cycles duration, N (%)				0.544
< 30 years	310 (27.0)	295 (26.3)	15 (33.3)	
30–40 years	783 (67.2)	755 (67.4)	28 (62.2)	
> 40 years	73 (6.3)	71 (6.3)	2 (4.4)	
HRT use, N (%)				0.995
No	1062 (77.0)	1022 (77.0)	40 (76.9)	
Yes	318 (23.0)	306 (23.0)	12 (23.1)	
Hysterectomy, N (%)				0.748
No	954 (69.1)	917 (69.1)	37 (71.2)	
Yes	426 (30.9)	411 (31.0)	15 (28.9)	
Thyroid medication, N (%)				0.428
No	1271 (92.1)	1221 (91.9)	50 (96.2)	
Yes	109 (7.9)	107 (8.1)	2 (3.9)	

BMI Body mass index, HRT hormone replacement therapy, DXA dual-energy X-ray absorptiometry.

Table 2
Hazard Ratios (HRs) of breast cancer risk according to quartiles of bone mineral density by DXA at the lumbar spine.

	DXA	Cases	Basic model[a]	Fully adjusted model[b]
Measurement for BMD	(g/cm^2)	N	HR (95% CI)	HR (95% CI)
1st quartile	< 0.83	17	1 (ref.)	1 (ref.)
2nd quartile	0.83–0.925	10	0.548 (0.249–1.207)	0.555 (0.251–1.228)
3rd quartile	0.926–1.033	11	0.606 (0.279–1.316)	0.623 (0.284–1.367)
4th quartile	> 1.033	14	0.754 (0.358–1.587)	0.787 (0.364–1.701)

BMD bone mineral density, DXA dual-energy X-ray absorptiometry.
[a] Adjusted for age at recruitment.
[b] Stratified for smoking status and menopausal status and adjusted for age at recruitment, sport, BMI and HRT use.

significantly reduced at higher quartiles of BMD (for example, HR 0.79, 95% CI: 0.36–1.70 for the 4th quartile in the fully adjusted model). The results for DXA z-scores adjusted for different variables are shown in Table 3. In the fully adjusted model, DXA z-scores were non-significantly associated with reduced breast cancer risk (HR 0.91, 95% CI 0.67–1.23). Adjustment for different potential confounders did not substantially influence the estimates.

3.1. Meta-analysis

Our database search rendered 987 hits (most related to breast cancer metastasis or treatment) of which 24 were retrieved for eligibility with BMD as potential risk factor (Fig. 1). In addition, the

Table 3
Hazard Ratios (HRs) of breast cancer risk for z-score of DXA at the lumbar spine adjusted for different confounders.

BMD measurement	N	HR (per 1 z-score increase)	95% CI
DXA			
Adjusted for age	1380	0.892	0.665–1.196
+ BMI	1363	0.913	0.913–1.234
+ sports	1380	0.893	0.667–1.198
+ smoking status	1379	0.892	0.665–1.196
+ menses	1166	0.902	0.657–1.239
+ HRT use	1380	0.892	0.665–1.196
+ Thyroid medication	1380	0.891	0.665–1.196
+ Hysterectomy	1380	0.894	0.666–1.199
Fully adjusted model[a]	1362	0.908	0.670–1.230

BMD bone mineral density, DXA dual-energy X-ray absorptiometry.
[a] Stratified for smoking status and menopausal status and adjusted for age at recruitment, sport, BMI and HRT use.

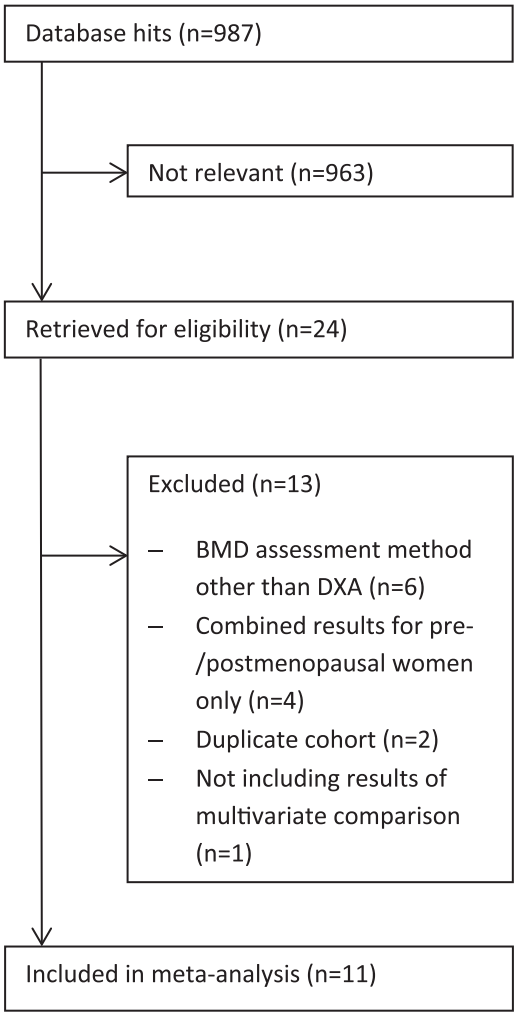


Fig. 1. Flow diagram of study selection.

references lists were screened for further relevant publications but did not provide any such.

Of those 24 publications, we excluded six due to a method other than DXA: the MABOT study due to quantitative ultrasonometry (Hadji et al., 2007), the NHANHES I and the Framingham study due to Osteo Gram Radiographic Absorptiometry (Nelson et al., 2002; Zhang et al., 1997), and the Study of Osteoporotic Fractures (SOF) using single-photon absorptiometry (Kuller et al., 1997; Lucas et al., 1998; Zmuda et al., 2001).

Table 4
Characteristics of the studies included in the meta-analysis.

Study	Cohort	Design	Follow-up (years)	Position	Mean age (years)	Total n	Cases n	Adjusted for
Present study	Women 50 +	PC	16.3	LS	55.5	1380	52	Age, BMI, physical activity, smoking, HRT
Kim et al., 2014	Samsung Medical Center, South Korea	CC	na	FN, LS	59.2	306	102	Age, BMI, height, smoking, alcohol, family history, HRT, parity
Grenier et al., 2011	Manitoba BMD register, Canada	PC	5.4	FN, LS	64.7	37,860	794	Age, BMI, HRT, corticosteroid use
Burshell et al., 2008	MORE and CORE trials	PC	6.0	FN, LS	66.5	2576	58	Age
Chen et al., 2008	Women's Health Initiative (WHI), US	PC	8.4	TH	63.0	9941	327	Age, education, BMI, smoking, alcohol, HRT, ethnicity, GAIL-Score
Kritz-Silverstein et al., 2006	San Diego community, US	CC		FN, LS	71.8	237	79	Age, physical activity, waist circumference, vitamin D intake
Ganry et al., 2004	Epidémiologie de l'ostéoporose (EPIDOS), France	PC	7.0	FN	79.4	1504	45	Age, education, BMI, smoking, alcohol, physical activity, HRT, age at menopause, parity, surgical menopause, calcium intake, breast feeding, family income
van der Klift et al., 2003	Rotterdam Study, Netherlands	PC	6.5	FN, LS	68.0	3107	74	Age
Ganry et al., 2001	Study of osteoporotic fractures of Picardie area, France	CC	na	FN, LS	58.4	252	126	Age, BMI, smoking, alcohol, family history, parity, age at menarche, age at menopause, calcium intake, breast feeding, diabetes, osteoporosis
Buist et al., 2001a, 2001b	Women screened for inclusion in the Fracture Intervention Trial (FIT), US	PC	3.7	TH	68.2	8203	131	Age, BMI, geographic area
Nguyen et al., 2000	Dubbo Osteoporosis Epidemiology Study (DOES), Australia	CC	na	FN, LS	67.6	150	30	Age, BMI, HRT, age at menarche, age at menopause
Cauley et al., 1996	Study of Osteoporotic Fractures (SOF), US	PC	3.2	LS, TH	71.5	6854	97	History of benign breast disease

PC: prospective cohort study; CC: case control study. FN: femoral neck; TH: total hip; LS: lumbar spine. BMI: body mass index; HRT: hormone replacement therapy.

Among the remaining 18 publications, we identified two with data of the Fracture Intervention Trial (FIT) (Buist et al., 2001b; Buist et al., 2001a), one using the full cohort (Buist et al., 2001b) and one using a nested case control design (Buist et al., 2001a), results of only the former of which were included in the meta-analysis. Likewise, we found two publications of the MORE and CORE trials (Cauley et al., 2007; Burshell et al., 2008), of the more recent of which we used the results of the placebo arm (Burshell et al., 2008). Further studies were excluded that reported only combined results for pre- and post-menopausal women (Fraenkel et al., 2013; Kerlikowske et al., 2005; Stewart et al., 2005; Trémollieres et al., 2008), or did not report multivariate results comparing cases and controls (Kalder et al., 2011). The characteristics of all 11 publications included in the meta-analysis are listed in Table 4. Results of these studies were combined with the results of our study.

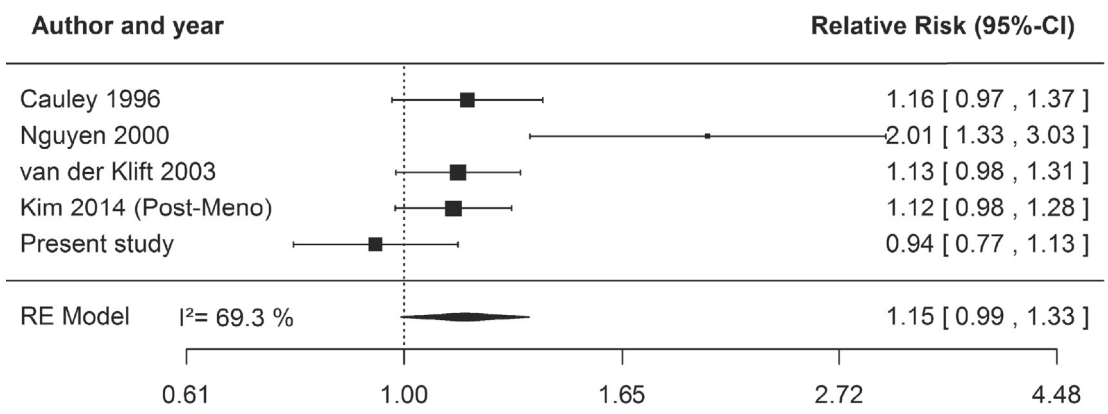
The results of the meta-analysis for continuous and categorical BMD at different measurement sites are shown in Fig. 2a–d. The combined risk ratio (RR) for BMD measurements of the lumbar spine revealed a 15% (95% CI 0.99–1.33) increase in breast cancer risk per 0.1 g/m^2 increase in BMD that just barely failed to reach statistical significance. For BMD at the femoral neck or total hip, however, a statistically significant 16% (95% CI 1.02–1.32) increase in breast cancer risk was found. When the highest BMD category was compared versus the lowest, BMD was associated with increased breast cancer risk independent of the measurement site. The combined RRs for comparison of the extreme BMD categories (highest vs. lowest) were 1.49 (95% CI 1.04–2.13) for the lumbar spine and 1.66 (95% CI 1.26–2.18) for the femoral neck or total hip. The I^2 values were in the range of 43.8% and 69.3% indicating moderate heterogeneity between the studies.

4. Discussion

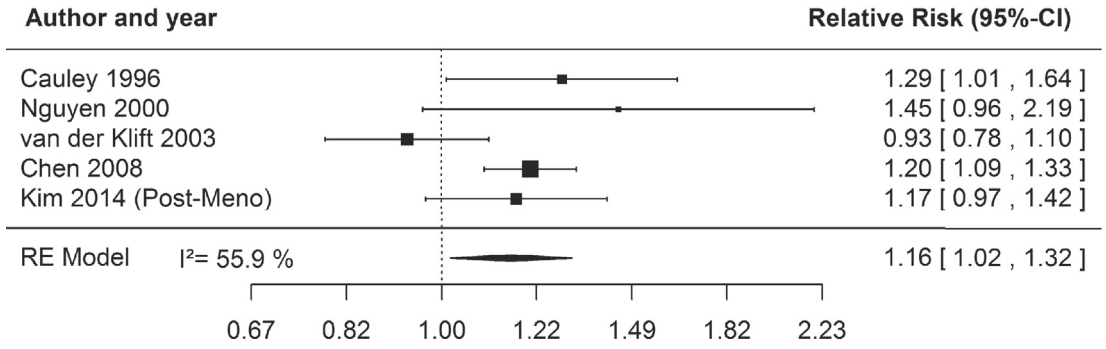
In this prospective cohort study, we found no indication for an association between BMD and breast cancer risk during 16.3 years of mean follow-up. While this finding is borne out by a number of previous studies (Kerlikowske et al., 2005; Cauley et al., 2007; Stewart et al., 2005; Trémollieres et al., 2008), other studies did find an association between BMD measured by DXA at the lumbar spine and breast cancer risk (Cauley et al., 1996; Chen et al., 2008; Ganry et al., 2001; Grenier et al., 2011). Moreover, the results of our meta-analysis including our data support the hypothesis that BMD is positively associated with breast cancer risk.

Different inclusion criteria, age patterns and follow-up intervals as well as differences in the adjustment for confounding variables may have contributed to divergent findings. For example, Grenier et al. (2011) used data of women aged ≥ 50 years from the Manitoba BMD database, and data from clinical trials including women with low BMD were used in other studies (Cauley et al., 2007; Burshell et al., 2008). Referrals to BMD measurement may be confounded by unmeasured factors such as medication or vitamin D levels affecting breast cancer risk that were not controlled for in the analyses. In contrast, in our population-based study, women participated in an additive health prevention program (Concin et al., 2002) where many younger patients not suspected at high risk for fracture were referred to DXA. Therefore, women in our study are likely to be at lower risk for breast cancer than in most previous investigations that included older women on average with an indication for low bone mass. In this regard, risk estimates shown for the BMD at the femoral neck in the population-based Rotterdam Study (van der Klift et al., 2003) are quite similar to our results.

Since estrogen is a major regulator of bone metabolism (Khosla et al., 2012) with an influence on breast cancer risk (Kaaks et al., 2005), and associations of insulin like growth factors (IGF) and vitamin D with both BMD and breast cancer have been reported (Adami et al., 2010; Rinaldi et al., 2006; Feldman et al., 2014), a biological link between BMD and breast cancer risk is plausible. In fact, Grenier et al. (2011) found that among women ≥ 50 years BMD of the lumbar spine was an independent risk factor for breast cancer, in particular if tumors were



a. Continuous lumbar spine, per 0.1 g/m² increase



b. Continuous femoral neck or total hip, per 0.1 g/m² increase

Fig. 2. a–d: Meta-analysis of BMD by DXA continuous (a, b) and categorical (c, d) by measurement site (lumbar spine a, c and femoral neck b, d) with breast cancer risk using the random-effects (RE) model.

estrogen-receptor (ER) positive (Grenier et al., 2011), and post-menopausal non-osteoporotic women with low bone mass were reported to be at higher breast cancer risk than postmenopausal osteoporotic patients (Burshell et al., 2008).

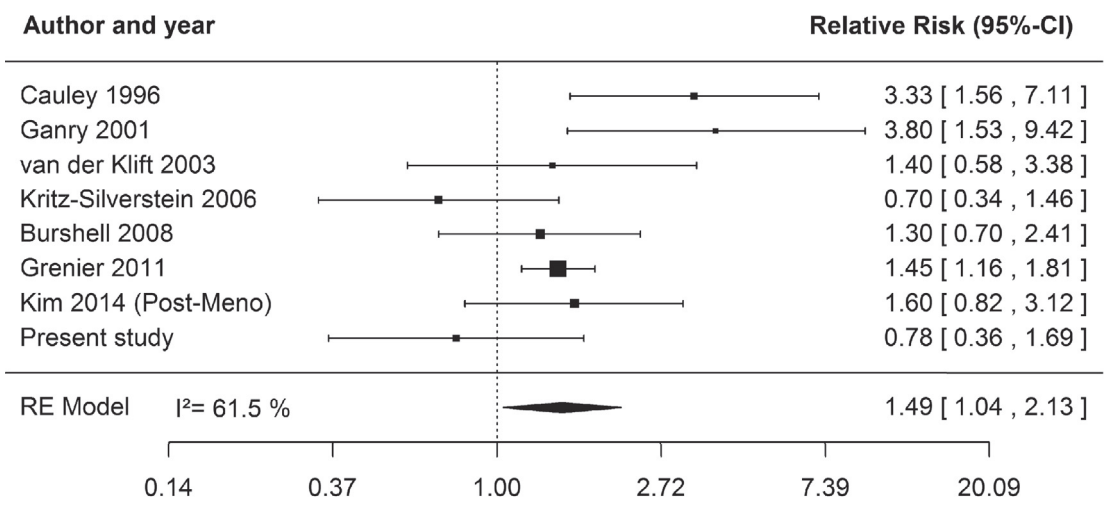
A strength of our study is the inclusion of a relatively homogenous age group at the baseline assessment and virtually complete long-term follow-up of > 16 years. By contrast, one limitation is the possible measurement error of BMD by DXA. However, the measurements were performed at one clinic and potential confounders were considered in the analyses. Another limitation is that our study is arguably not representative of the general Austrian population, because participation in the health check-ups was voluntary, which could have led to the healthy volunteer bias. Even though we had no information on vitamin D and hormone-receptor status, information on drugs was available and so we could consider thyroid medication as co-factor in the models, whereas use of corticoids was reported by too few women (N = 2) to be included in our analyses. A previous investigation reported that about 76% of breast cancers had a positive hormone estrogen receptor (ER) status (Dunnwald et al., 2007). Unfortunately, we had no information on hormone receptor status, but the prevalence of ER positive breast cancer cases is likely to be similar. However, residual confounding could have affected our results.

The results of the meta-analysis are in line with a previous report on the results of 10 prospective studies (Qu et al., 2013) showing that women per 1 SD increase in BMD of the hip or spine have a 20% or 26% increased breast cancer risk. In our up-dated meta-analysis including more studies, we found a borderline statistically significant 16% increase in breast cancer risk for the BMD at the femoral neck and 15% for BMD at the lumbar spine.

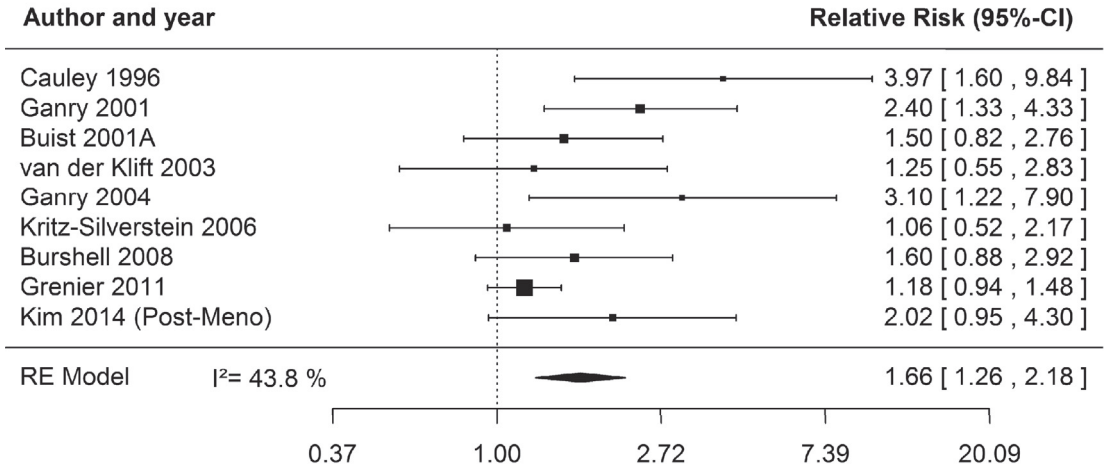
Most of the included studies reported on BMD measurement by DXA of both measurement sites, i.e. the lumbar spine and femoral neck (Cauley et al., 1996; Burshell et al., 2008; Ganry et al., 2001, 29; Grenier et al., 2011; van der Klift et al., 2003; Kritz-Silverstein et al., 2006; Kim et al., 2014). Our finding of a stronger association for the comparison the extreme categories of BMD measured at the femoral neck/total hip than the lumbar spine is somehow in contrast with previous results (Qu et al., 2013). However, for the continuous values we found no differences between the site of measurement.

Interpretation of the results of our meta-analysis needs to consider several limitations. Based on the funnel plots, we found little indication for publication bias, but the quality of the included studies varies. Some investigations were based on secondary data analysis (Grenier et al., 2011), clinical trials (Cauley et al., 2007; Burshell et al., 2008), and cohort studies (Chen et al., 2008; Zhang et al., 1997; van der Klift et al., 2003), and adjustment for potential confounding variables differed between publications. Only few studies considered history of benign breast disease (Cauley et al., 1996), history of osteoporosis (Ganry et al., 2001), calcium (Ganry et al., 2001) or vitamin D intake (Kritz-Silverstein et al., 2006) as covariates. Cancer detection methods may have changed over time and may differ between investigations. Moreover, methodological differences could have introduced heterogeneity. However, the calculation of I^2 indicated moderate heterogeneity for continuous BMD values measured at the femoral neck and the lumbar spine. In addition, the calculation of subgroups of measurement site revealed similar results.

In conclusion, we found no significant association between BMD



c. Categorical lumbar spine, highest versus lowest category



d. Categorical femoral neck or total hip, highest versus lowest category

Fig. 2. (*continued*)

measured by DXA and breast cancer risk in a population-based cohort of women at mean age of 55 years and long-term follow-up. However, overall the present meta-analysis extends and confirms the association between increasing BMD and increased breast cancer risk in post-menopausal women. The strength of association depended on the measurement site and was slightly stronger when measured at the total hip.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bonr.2017.09.004.

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Conflict of interest

Gabriele Nagel, Raphael S Peter, Eva Klotz, Wolfgang Brozek and Hans Concin declare that they have no conflict of interest.

References

Adami, S., Zivelonghi, A., Braga, V., Fracassi, E., Gatti, D., Rossini, M., Ulivieri, F.M., Viapiana, O., 2010. Insulin-like growth factor-1 is associated with bone formation markers, PTH and bone mineral density in healthy premenopausal women. Bone 46, 244–247. http://dx.doi.org/10.1016/j.bone.2009.10.011.

Arnold, M., Karim-Kos, H.E., Coebergh, J.W., Byrnes, G., Antilla, A., Ferlay, J., Renehan, A.G., Forman, D., Soerjomataram, I., 2015. Recent trends in incidence of five common cancers in 26 European countries since 1988: analysis of the European Cancer Observatory. Eur. J. Cancer 51, 1164–1187. http://dx.doi.org/10.1016/j.ejca.2013.09.002.

Buist, D.S., LaCroix, A.Z., Barlow, W.E., White, E., Cauley, J.A., Bauer, D.C., Weiss, N.S., 2001a. Bone mineral density and endogenous hormones and risk of breast cancer in postmenopausal women (United States). Cancer Causes Control 12, 213–222.

Buist, D.S., LaCroix, A.Z., Barlow, W.E., White, E., Weiss, N.S., 2001b. Bone mineral density and breast cancer risk in postmenopausal women. J. Clin. Epidemiol. 54, 417–422.

Burshell, A.L., Song, J., Dowsett, S.A., Mershon, J.L., Delmas, P.D., Secrest, R.J., Cauley, J.A., 2008. Relationship between bone mass, invasive breast cancer incidence and raloxifene therapy in postmenopausal women with low bone mass or osteoporosis. Curr. Med. Res. Opin. 24, 807–813. http://dx.doi.org/10.1185/030079908X273282.

Cauley, J.A., Lucas, F.L., Kuller, L.H., Vogt, M.T., Browner, W.S., Cummings, S.R., 1996. Bone mineral density and risk of breast cancer in older women: the study of

osteoporotic fractures. Study of Osteoporotic Fractures Research Group. JAMA 276, 1404–1408.
Cauley, J.A., Song, J., Dowsett, S.A., Mershon, J.L., Cummings, S.R., 2007. Risk factors for breast cancer in older women: the relative contribution of bone mineral density and other established risk factors. Breast Cancer Res. Treat. 102, 181–188. http://dx.doi.org/10.1007/s10549-006-9326-5.
Chen, Z., Arendell, L., Aickin, M., Cauley, J., Lewis, C.E., Chlebowski, R., 2008. Hip bone density predicts breast cancer risk independently of Gail score: results from the Women's Health Initiative. Cancer 113, 907–915. http://dx.doi.org/10.1002/cncr.23674.
Concin, H., Ulmer, H., Hefler, L., 2002. Mental well-being in 5000 women participating in the "Women-Plus" preventive medicine program. Maturitas 41 (Suppl. 1), S9–12.
Dunnwald, L.K., Rossing, M.A., Li, C.I., 2007. Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients. Breast Cancer Res. 9, R6. http://dx.doi.org/10.1186/bcr1639.
Feldman, D., Krishnan, A.V., Swami, S., Giovannucci, E., Feldman, B.J., 2014. The role of vitamin D in reducing cancer risk and progression. Nat. Rev. Cancer 14, 342–357. http://dx.doi.org/10.1038/nrc3691.
Fraenkel, M., Novack, V., Liel, Y., Koretz, M., Siris, E., Norton, L., Shafat, T., Shany, S., Geffen, D.B., 2013. Association between bone mineral density and incidence of breast cancer. PLoS One 8, e70980. http://dx.doi.org/10.1371/journal.pone.0070980.
Ganry, O., Tramier, B., Fardellone, P., Raverdy, N., Dubreuil, A., 2001. High bone-mass density as a marker for breast cancer in post-menopausal women. Breast 10, 313–317. http://dx.doi.org/10.1054/brst.2000.0247.
Ganry, O., Baudoin, C., Fardellone, P., Peng, J., Raverdy, N., 2004. Bone mass density and risk of breast cancer and survival in older women. Eur. J. Epidemiol. 19, 785–792.
Grenier, D., Cooke, A.L., Lix, L., Metge, C., Lu, H., Leslie, W.D., 2011. Bone mineral density and risk of postmenopausal breast cancer. Breast Cancer Res. Treat. 126, 679–686. http://dx.doi.org/10.1007/s10549-010-1138-y.
Hadji, P., Gottschalk, M., Ziller, V., Kalder, M., Jackisch, C., Wagner, U., 2007. 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 56, 312–321. http://dx.doi.org/10.1016/j.maturitas.2006.09.005.
Harvey, N., Dennison, E., Cooper, C., 2010. Osteoporosis: impact on health and economics. Nat. Rev. Rheumatol. 6, 99–105. http://dx.doi.org/10.1038/nrrheum.2009.260.
Hernlund, E., Svedbom, A., Ivergård, M., Compston, J., Cooper, C., Stenmark, J., McCloskey, E.V., Jönsson, B., Kanis, J.A., 2013. 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. 8, 136. http://dx.doi.org/10.1007/s11657-013-0136-1.
Higgins, J.P.T., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. BMJ 327, 557–560. http://dx.doi.org/10.1136/bmj.327.7414.557.
Howell, A., Anderson, A.S., Clarke, R.B., Duffy, S.W., Evans, D.G., Garcia-Closas, M., Gescher, A.J., Key, T.J., Saxton, J.M., Harvie, M.N., 2014. Risk determination and prevention of breast cancer. Breast Cancer Res. 16, 446. http://dx.doi.org/10.1186/s13058-014-0446-2.
Kaaks, R., Rinaldi, S., Key, T.J., Berrino, F., Peeters, P.H.M., Biessy, C., Dossus, L., Lukanova, A., Bingham, S., Khaw, K.-T., Allen, N.E., Bueno-de-Mesquita, H.B., van Gils, C.H., Grobbee, D., Boeing, H., Lahmann, P.H., Nagel, G., Chang-Claude, J., Clavel-Chapelon, F., Fournier, A., Thiébaut, A., González, C.A., Quirós, J.R., Tormo, M.-J., Ardanaz, E., Amiano, P., Krogh, V., Palli, D., Panico, S., Tumino, R., Vineis, P., Trichopoulou, A., Kalapothaki, V., Trichopoulos, D., Ferrari, P., Norat, T., Saracci, R., Riboli, E., 2005. Postmenopausal serum androgens, oestrogens and breast cancer risk: the European prospective investigation into cancer and nutrition. Endocr. Relat. Cancer 12, 1071–1082. http://dx.doi.org/10.1677/erc.1.01038.
Kalder, M., Jäger, C., Seker-Pektas, B., Dinas, K., Kyvernitakis, I., Hadji, P., 2011. Breast cancer and bone mineral density: the Marburg Breast Cancer and Osteoporosis Trial (MABOT II). Climacteric 14, 352–361. http://dx.doi.org/10.3109/13697137.2011.557754.
Kerlikowske, K., Shepherd, J., Creasman, J., Tice, J.A., Ziv, E., Cummings, S.R., 2005. Are breast density and bone mineral density independent risk factors for breast cancer? J. Natl. Cancer Inst. 97, 368–374. http://dx.doi.org/10.1093/jnci/dji056.
Khosla, S., 2010. Update on estrogens and the skeleton. J. Clin. Endocrinol. Metab. 95, 3569–3577. http://dx.doi.org/10.1210/jc.2010-0856.
Khosla, S., Oursler, M.J., Monroe, D.G., 2012. Estrogen and the skeleton. Trends Endocrinol. Metab. 23, 576–581. http://dx.doi.org/10.1016/j.tem.2012.03.008.
Kim, B.-K., Choi, Y.-H., Song, Y.-M., Park, J.-H., Noh, H.-M., Nguyen, T.L., Hopper, J.L., 2014. Bone mineral density and the risk of breast cancer: a case-control study of Korean women. Ann. Epidemiol. 24, 222–227. http://dx.doi.org/10.1016/j.annepidem.2013.11.009.
van der Klift, M., de Laet, C.E.D.H., Coebergh, J.W.W., Hofman, A., Pols, H.A.P., 2003. Bone mineral density and the risk of breast cancer: the Rotterdam Study. Bone 32, 211–216.
Kritz-Silverstein, D., Schneider, D.L., Sandwell, J., 2006. Breast cancer and bone mass in older women: is bone density prescreening for mammography useful? Osteoporos. Int. 17, 1196–1201. http://dx.doi.org/10.1007/s00198-006-0124-z.
Kuller, L.H., Cauley, J.A., Lucas, L., Cummings, S., Browner, W.S., 1997. Sex steroid hormones, bone mineral density, and risk of breast cancer. Environ. Health Perspect. 105 (Suppl. 3), 593–599.
Lucas, F.L., Cauley, J.A., Stone, R.A., Cummings, S.R., Vogt, M.T., Weissfeld, J.L., Kuller, L.H., 1998. Bone mineral density and risk of breast cancer: differences by family history of breast cancer. Study of Osteoporotic Fractures Research Group. Am. J. Epidemiol. 148, 22–29.
Nelson, R.L., Turyk, M., Kim, J., Persky, V., 2002. Bone mineral density and the subsequent risk of cancer in the NHANES I follow-up cohort. BMC Cancer 2, 22.
Nguyen, T.V., Center, J.R., Eisman, J.A., 2000. Association between breast cancer and bone mineral density: the Dubbo Osteoporosis Epidemiology Study. Maturitas 36, 27–34.
Qu, X., Zhang, X., Qin, A., Liu, G., Zhai, Z., Hao, Y., Li, H., Zhu, Z., Dai, K., 2013. Bone mineral density and risk of breast cancer in postmenopausal women. Breast Cancer Res. Treat. 138, 261–271. http://dx.doi.org/10.1007/s10549-013-2431-3.
Rinaldi, S., Peeters, P.H.M., Berrino, F., Dossus, L., Biessy, C., Olsen, A., Tjonneland, A., Overvad, K., Clavel-Chapelon, F., Boutron-Ruault, M.C., Téhard, B., Nagel, G., Linseisen, J., Boeing, H., Lahmann, P.H., Trichopoulou, A., Trichopoulos, D., Koliva, M., Palli, D., Panico, S., Tumino, R., Sacerdote, C., van Gils, C.H., van Noord, P., Grobbee, D.E., Bueno-de-Mesquita, H.B., Gonzalez, C.A., Agudo, A., Chirlaque, M.D., Barricarte, A., Larrañaga, N., Quiros, J.R., Bingham, S., Khaw, K.T., Key, T., Allen, N.E., Lukanova, A., Slimani, N., Saracci, R., Riboli, E., Kaaks, R., 2006. IGF-I, IGFBP-3 and breast cancer risk in women: the European Prospective Investigation into Cancer and Nutrition (EPIC). Endocr. Relat. Cancer 13, 593–605. http://dx.doi.org/10.1677/erc.1.01150.
Santen, R.J., Yue, W., Wang, J.-P., 2015. Estrogen metabolites and breast cancer. Steroids 99, 61–66. http://dx.doi.org/10.1016/j.steroids.2014.08.003.
Stewart, A., Kumar, V., Torgerson, D.J., Fraser, W.D., Gilbert, F.J., Reid, D.M., 2005. Axial BMD, change in BMD and bone turnover do not predict breast cancer incidence in early postmenopausal women. Osteoporos. Int. 16, 1627–1632. http://dx.doi.org/10.1007/s00198-005-1886-4.
Trémollieres, F.A., Pouillès, J.-M., Laparra, J., Ribot, C., 2008. Bone mineral density at menopause does not predict breast cancer incidence. Osteoporos. Int. 19, 1497–1504. http://dx.doi.org/10.1007/s00198-008-0596-0.
Zhang, Y., Kiel, D.P., Kreger, B.E., Cupples, L.A., Ellison, R.C., Dorgan, J.F., Schatzkin, A., Levy, D., Felson, D.T., 1997. Bone mass and the risk of breast cancer among postmenopausal women. N. Engl. J. Med. 336, 611–617. http://dx.doi.org/10.1056/NEJM199702273360903.
Zmuda, J.M., Cauley, J.A., Ljung, B.M., Bauer, D.C., Cummings, S.R., Kuller, L.H., Study of Osteoporotic Fractures Research Group, 2001. Bone mass and breast cancer risk in older women: differences by stage at diagnosis. J. Natl. Cancer Inst. 93, 930–936.