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Is There an Association Between Bone Mineral Density and Mammographic Density? A Systematic Review

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Abstract

Introduction: Both bone mineral density (BMD) and breast density are related to reproductive hormone levels. This suggests that BMD and breast density could be meaningfully associated, and serve as surrogate markers for breast cancer risk. However, few studies have investigated the association of BMD with percent mammographic density, making it difficult to draw meaningful conclusions.
Materials and Methods: We conducted a systematic review of studies published in electronic databases till April 2016 using the following search terms: ''bone density,'' ''bone mineral density,'' ''mammographic breast density,'' ''breast density,'' and ''mammographic density.'' We identified 203 articles, of which 8 met the inclusion criteria for this review.
Results: BMD does not appear to be associated with percent mammographic density. BMD at the spine was weakly positively associated with percent mammographic density among postmenopausal women who were not hormone users, while BMD at the hip and legs was positively associated with percent mammographic density among premenopausal women. On the other hand, one study reported an inverse association of BMD at the spine and hip with percent mammographic density among perimenopausal women.
Conclusion: In this review, we found no evidence of an association between BMD and percent mammographic density.

Keywords: bone mineral density (BMD), mammographic density, menopause

Introduction

Mammographic density is a strong risk factor for breast cancer. An increased breast density is associated with a four- to sixfold increased risk of breast cancer.[1–4] Likewise, some studies have suggested that increased bone mineral density (BMD) might be associated with an increased risk of breast cancer, especially among postmenopausal women.[5,6] Although the underlying mechanisms are still poorly understood, hormonal exposure is thought to play an important role in driving the association of mammographic density with breast cancer risk.[7–10] In the Women's Health Initiative (WHI) trial, 1 year of estrogen plus progestin use was associated with a 6% increase in mammographic density.[11] Hormonal exposure also plays an important role in BMD.[12,13] Longer duration of exposure to estrogen is positively associated with BMD.[14–16] Estrogen deficiency during menopause induces cortical bone loss by inhibiting bone resorption activity, resulting in decreased bone mass.[17–19] Hence, it is possible that similar etiological pathways involving reproductive hormone exposure may drive the association of mammographic density and BMD with breast cancer risk. On the other hand, adiposity, which is a risk factor for postmenopausal breast cancer (but inversely associated with premenopausal breast cancer), has divergent effects on mammographic density and BMD.[20,21] While body mass index (BMI) is positively associated with BMD,[22,23] it is inversely associated with mammographic density.[24,25] Therefore, the association of BMD with percent mammographic density may be more complex.

Understanding the association of BMD with percent mammographic density might provide better knowledge of how breast cancer intermediaries increase breast cancer risk. Furthermore, if mammographic density is associated with BMD, knowing a woman's breast density might have some utility in predicting BMD, and possibly future fracture risk since BMD is a strong predictor of future fracture risk.[26] The

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few studies that have investigated the association of BMD with percent mammographic density,[27–34] have produced conflicting results, and no review of the topic has been undertaken. To extend knowledge on the association of BMD with percent mammographic density, we conducted a systematic review of published studies.

Materials and Methods

We identified studies published between January 2000 and April 2016 using the following databases: PubMed, OVidSP, BioMed Central, EMBASE, Web of Science, and Scopus. Search terms included the following: ''bone density,'' ''bone mineral density,'' ''mammographic breast density,'' ''breast density,'' and ''mammographic density.'' Search queries in the databases yielded 211 articles (Figure 1). Abstracts and results were examined if the articles were relevant to our topic of study. Reference lists of relevant articles were also examined.

From 211 articles, we included studies if they met the following criteria: reported on (1) the association of BMD with percent mammographic density. Hence, studies using Breast Imaging-Reporting and Data System (BI-RADS) classification were not included. The exposure was defined as BMD, while the outcome was defined as percent mammographic density. (2) Publications were in English language. Eight studies met the inclusion criteria. From these eight articles, we extracted information on study design, age, menopausal status, and number of participants, BMD sites, and confounders. Studies were available on the following BMD sites in relation to mammographic density: spine ($N=7$), hip ($N=6$), and other sites, including arms, ribs, and overall body ($N=3$). We extracted data on beta coefficient values, 95% confidence intervals (CIs), and *p*-values from the original studies.

Results

BMD at the spine

Seven studies have investigated the association of BMD at the spine with percent mammographic density[27–33] (Table 1). No associations were reported in studies that did not stratify by menopausal status. BMD of the spine was associated with percent mammographic density in two studies of the five studies that stratified by menopausal status. Crandall et al. reported a very weak positive association between BMD at the spine ($\beta=0.099$, $p=0.08$) and percent mammographic density among postmenopausal women who were not recent hormone users after adjusting for age, BMI, and cigarette smoking.[29] In another study, the same authors observed an inverse association between BMD at the spine ($\beta=-20.6$ [95% CI: –37.2 to –3.9], $p<0.05$) and mammographic density among early perimenopausal women.[30]

BMD at the hip

Six studies have investigated the association of BMD at the hip with percent mammographic density[27,29–33] (Table 2). The studies that investigated associations among all women regardless of menopausal status reported no association.[27,31,33] Five studies stratified their analyses by menopausal status. BMD at the hip was positively associated with mammographic density in two studies: one among premenopausal women ($\beta=0.59$, $p<0.05$)[33] and one among postmenopausal women who were not recent hormone users ($\beta=0.156$, $p<0.05$).[29] Conversely, an inverse association was observed among early perimenopausal women ($\beta=-18.8$ [95% CI: –37.0 to –0.6], $p<0.05$).[30]

BMD at other sites (legs, ribs, arms, and whole body)

Only three studies have investigated the association of BMD at other sites, including ribs, arms, leg, and whole body, with mammographic density[28,33,34] and two studies reported no associations overall. However, Sung et al. observed a positive association of BMD at the legs with mammographic density among premenopausal women ($\beta=0.59$, $p<0.05$)[33] (Table 3). A recent study observed a positive association of BMD at the forearm with percent mammographic density

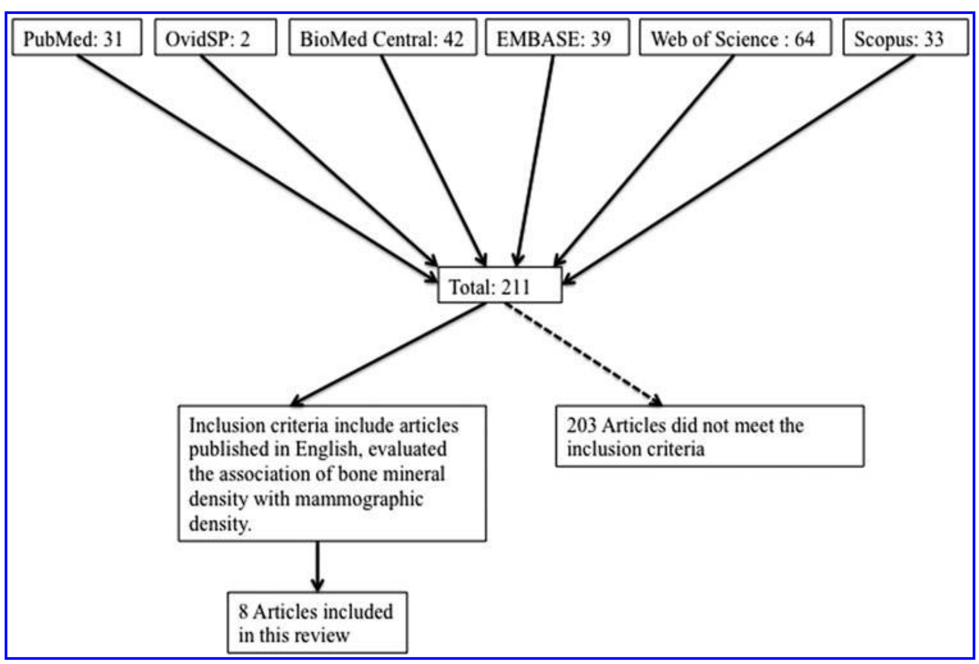

FIG. 1. Flow diagram of the literature search.

Table 1. Summary Description of Studies on the Association of Bone Mineral Density at the Spine with Percent Mammographic Breast Density

Reference, country	*Design*	*Age (years)*	*Study participants*	*Results (β coefficient or correlation)*	*95% Confidence interval/*p	*Confounders*
Sung et al.,[33] Korea	Cross-sectional	≥30	Overall (N = 730)	$\beta = 0.27$[a]	–0.01 to 0.55	Age, smoking status, alcohol consumption, physical exercise, number of live children, age at menarche, age at birth of first child, duration of breast feeding, use of oral contraceptives, hormone replacement therapy
			Premenopausal (N = 462)	$\beta = 0.21$[a]	–0.0 to 0.46	
			Postmenopausal (N = 268)	$\beta = 0.42$[a]	–0.27 to 1.11	
Gupta et al.,[32] Kuwait	Cross-sectional	25–74	Premenopausal (N = 147)	r = 0.158[b]	0.125	Ethnicity
			Postmenopausal (N = 96)	r = 0.021[b]	0.798	
Crandall et al.,[30] United States	Cross-sectional	42–52	Early Perimenopausal (N = 249)	$\beta = -20.6$[c]	0.02	Age, BMI, ethnicity, study site, number of pregnancies, alcohol consumption, age at first childbirth, smoking status, physical activity score
			Premenopausal (N = 56)	$\beta = -29.0$[c]	0.23	
Dite et al.,[27] Australia	Cross-sectional	N/A	Overall (N = 268)	$\beta = -0.02$[d]	0.79	Age, BMI, smoking status
			Premenopausal (N = N/A)	$\beta = -0.10$[d]	0.33	
			Postmenopausal/past or never HT (N = N/A)	$\beta = 0.02$[d]	0.85	
			Postmenopausal/current or recent HT users (N = N/A)	$\beta = 0.24$[d]	0.19	
Dite et al.,[28] Australia	Longitudinal	38–71	Overall (N = 134)	r = 0.015[e]	0.8	Age at mammogram, age at bone scan, height and weight
Crandall et al.,[29] United States	Cross-sectional	45–64	Postmenopausal women who are not recent HT users (N = 417)	$\beta = 0.099$[d]	0.08	Age, BMI, smoking status
			Postmenopausal women who are recent HT users (N = 173)	$\beta = -0.065$[d]	0.44	
Kerlikowske et al.,[31] United States	Cross-sectional and nested case-control study	≥28	Overall (N = 405)	r = 0.01[f]	0.87	Age, BMI, ethnicity, age at first live birth, HT use
			Premenopausal (N = 20)	r = 0.09[f]	0.71	
			Postmenopausal/past or never HT (N = 142)	r = 0.06[f]	0.48	
			Postmenopausal/current or recent HT (N = 153)	r = 0.00[f]	1.00	

[a]Beta coefficients assessed by a linear mixed model.
[b]Spearman's correlation coefficient.
[c]Beta coefficients assessed by a linear regression model. Current/recent hormone users were excluded in this model.
[d]Beta coefficients assessed by a linear regression model.
[e]Cross-trait cross-twin correlations.
[f]Pearson's correlation coefficient.
BMI, body mass index; HT, hormone therapy; N/A, not available.

Table 2. Summary Description of Studies on the Association of Bone Mineral Density at the Hip with Percent Mammographic Breast Density

Reference, country	*Design*	*Age (years)*	*Study participants*	*Results (β coefficient or correlation)*	*95% Confidence interval/*p	*Confounders*
Sung et al.,[33] Korea	Cross-sectional	≥30	Overall (N = 730)	$\beta = 0.75^{a}$	0.30 to 1.21	Age, smoking status, alcohol consumption, physical exercise, number of live children, age at menarche, age at birth of first child, duration of breast feeding, use of oral contraceptives, hormone replacement therapy
			Premenopausal (N = 462)	$\beta = 0.59^{a}$	0.16 to 1.02	
			Postmenopausal (N = 268)	$\beta = 0.45^{a}$	–0.46 to 1.36	
Gupta et al.,[32] Kuwait	Cross-sectional	25–74	Premenopausal (N = 147)	$r = 0.094^{b}$	0.385	Ethnicity
			Postmenopausal (N = 96)	$r = 0.082^{b}$	0.342	
Crandall et al.,[30] United States	Cross-sectional	42–52	Early Perimenopausal (N = 301)	$\beta = -18.8^{c}$	0.04	Age, BMI, ethnicity, study site, number of pregnancies, alcohol consumption, age at first childbirth, smoking status, physical activity score
			Premenopausal (N = 80)	$\beta = 3.9^{c}$	0.87	
Dite et al.,[27] Australia	Cross-sectional	N/A	Overall (N = 268)	$\beta = -0.09^{d}$	0.41	Age, BMI, and smoking status
			Premenopausal (N = N/A)	$\beta = -0.23^{d}$	0.06	
			Postmenopausal/ past or never HT (N = N/A)	$\beta = 0.05^{d}$	0.78	
			Postmenopausal/ current or recent HT users (N = N/A)	$\beta = -0.07^{d}$	0.79	
Crandall et al.,[29] United States	Cross-sectional	45–64	Postmenopausal women who are not recent HT users (N = 417)	$\beta = 0.156^{d}$	0.04	Age, BMI, smoking status
			Postmenopausal women who are recent HT users (N = 173)	$\beta = -0.073^{d}$	0.51	
Kerlikowske et al.,[31] United States	Cross-sectional and nested case–control study	≥28	Overall (N = 424)	$r = -0.06^{e}$	0.22	Age, BMI, ethnicity, age at first live birth, HT use
			Premenopausal (N = 22)	$r = -0.00^{e}$	1.00	
			Postmenopausal/ past or never HT (N = 149)	$r = -0.11^{e}$	0.17	
			Postmenopausal/ current or recent HT (N = 158)	$r = -0.06^{e}$	0.47	

[a]Beta coefficients assessed by a linear mixed model.
[b]Spearman's correlation coefficient.
[c]Beta coefficients assessed by a linear regression model. Current/recent hormone users were included in this model.
[d]Beta coefficients assessed by a linear regression model.
[e]Pearson's correlation coefficient.

Table 3. Summary Description of Studies on the Association of Bone Mineral Density at Other Sites (Ribs, Arms, Body) with Percent Mammographic Breast Density

Reference, country	*Design*	*Age (years)*	*Study participants*	*Results (β coefficient or correlation)*	*95% Confidence interval/p*	*Confounders*
Moseson et al.,[34] Mexico	Prospective cohort study	N/A	Premenopausal ($N=955$)	Forearm (BMD: 0.41–0.45): 0.2[a]	−2.30 to 2.71	Family history of breast cancer, age at menarche, smoking, alcohol, hormone use, daily calcium intake, BMI, number of pregnancies, age at first pregnancy, contraceptive use
				Forearm (BMD: 0.45–0.48): −0.91[a]	−3.42 to 1.61	
				Forearm (BMD: 0.48+): −0.21[a]	−2.82 to 2.40	
			Postmenopausal ($N=552$)	Forearm (BMD: 0.35–0.40): 0.77[a]	−2.32 to 3.86	
				Forearm (BMD: 0.40–0.44): 5.06[a]	1.87 to 8.26	
				Forearm (BMD: 0.44+): 4.44[a]	1.11 to 7.77	
Sung et al.,[33] Korea	Cross-sectional	≥30	Overall ($N=730$)	Legs: $\beta=0.661$	0.16 to 1.15	Age, smoking status, alcohol consumption, physical exercise, number of live children, age at menarche, age at birth of first child, duration of breast feeding, use of oral contraceptives, hormone replacement therapy
			Premenopausal ($N=462$)	Legs: $\beta=0.59$[a]	0.05 to 1.14	
			Postmenopausal ($N=268$)	Legs: $\beta=0.39$[a]	−0.51 to 1.28	
			Overall ($N=730$)	Arms: $\beta=0.93$[a]	0.28 to 1.57	
			Premenopausal ($N=462$)	Arms: $\beta=0.43$[a]	−0.05 to 0.92	
			Postmenopausal ($N=268$)	Arms: $\beta=1.87$[a]	−0.09 to 3.82	
			Overall ($N=730$)	Ribs: $\beta=1.11$[a]	0.29 to 1.92	
			Premenopausal ($N=462$)	Ribs: $\beta=0.59$[a]	−0.07 to 1.24	
			Postmenopausal ($N=268$)	Ribs: $\beta=0.91$[a]	−1.53 to 3.36	
			Overall ($N=730$)	Whole body: $\beta=0.381$	−0.14 to 0.90	
			Premenopausal ($N=462$)	Whole body: $\beta=0.46$[a]	−0.10 to 1.03	
			Postmenopausal ($N=268$)	Whole body: $\beta=0.005$[a]	−0.89 to 0.90	
Dite et al.,[28] Australia	Longitudinal	38–71	Overall ($N=134$)	Arms: r = 0.0702	0.3	Age at mammogram, age at bone scan, height and weight
			Overall ($N=134$)	Neck: $r=-0.031$[b]	0.6	

[a]Beta coefficients assessed by a linear mixed model.
[b]Cross-trait cross-twin correlations.
BMD, bone mineral density.

among postmenopausal women, but not among premenopausal women (Table 3).

Discussion

In this review, we identified eight studies published up till April 2016 that evaluated the association of BMD with percent mammographic density. There is little evidence to support an association between BMD and percent mammographic density. However, there appears to be a weak association between BMD at the spine and hip and percent mammographic density, which may be modified by menopausal status. While BMD at the spine was weakly positively associated with percent mammographic density among postmenopausal women who were not hormone users, BMD at the spine and hip was weakly negatively associated with mammographic density among perimenopausal women. On the other hand, BMD at the hip and legs was weakly positively associated with percent mammographic density among premenopausal women. Since reproductive hormone changes across a menstrual cycle as well as across the menopausal transition,[35] it is possible that menopausal status, which affects reproductive hormone levels, modifies the effect of BMD on percent mammographic density.

Hormonal status, BMD, and mammographic density

A few of the studies observed a small, but statistically significant association of BMD on percent mammographic density after stratifying by menopausal status. This suggests that changes in reproductive hormone levels, particularly estrogen, over the course of the reproductive life cycle might moderate the association of BMD and percent mammographic density.

Estrogen levels in women decrease with aging.[36,37] The loss of ovarian estrogen during menopause is associated with a decline in BMD.[17,37] Postmenopausal women who use menopausal estrogen therapy for more than 7 years have higher BMD than those who had not taken estrogen therapy.[38] Furthermore, changes in reproductive hormones affect breast density as well,[7] although this appears mainly due to progesterone.[11] This increase in percent mammographic density was greater among postmenopausal women with the use of estrogen/progestin combination therapy, but not with the use of estrogen only.[39] Therefore, studies evaluating the associations of BMD with mammographic density need to consider hormonal status, with respect to menopausal status and use of menopausal hormonal therapy. Of the seven studies in this review, only four stratified their analyses by both menopausal status and use of menopausal hormonal therapy.[27,29–31]

Furthermore, because combined menopausal hormone therapy (estrogen plus progestin) impacts breast density rather than estrogen alone, it is important for future studies to specify what type of menopausal hormone therapy study participants used.

BMI, BMD, and mammographic density

There is a complex relationship between adiposity, breast cancer and breast cancer risk factors. Elevated BMI during the premenopausal years has a protective effect on premenopausal breast cancer, but during the postmenopausal years, elevated BMI is associated with increased breast cancer risk.[40,41] In addition, increased BMI is positively associated with BMD, but inversely associated with mammographic density.[42–44] For postmenopausal women, as BMI increases, estrogen levels increase due to the conversion of androgens to estrogen in adipose tissue.[45] In addition, a recently published study reported no association overall, but a positive association between BMD and percent mammographic density among obese women, and an inverse association among leaner women.[34] This suggests a complex association. Nevertheless, studies evaluating the association of BMD with percent mammographic density have not stratified their analyses by BMI, except for one conducted among Kuwaiti women.[32] It should be noted that one study not included in this review, because it reported breast density using the BI-RADS classification rather than percent mammographic density, reported a small, but significant negative association between BMD at hip and breast density among postmenopausal women with normal weight and no relationship in overweight or obese women.[46] Scattered fibroglandular densities and heterogeneously dense categories have wide percent mammographic density ranges and have large overlaps of percentage density in qualitative BI-RADS categories 2–4, and this may introduce limitations to their study.[47,48]

The limitations of this review need to be taken into consideration when interpreting the results. Because of the heterogeneity of studies and limited data on each BMD site, we performed a systematic review, rather than a meta-analysis, hence no additional statistical analyses were conducted.

In conclusion, there is no evidence to support an association between BMD and percent mammographic density. Any potential association is weak at best, which argues against the need for further studies.

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Author Disclosure Statement

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