RESEARCH ARTICLE

Bone Mineral Density and Breast Cancer Risk Factors among Premenopausal and Postmenopausal Women - A Systematic Review

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Abstract

Background: Bone mineral density (BMD) is a lifetime marker of estrogen in a woman's body and has been associated with increased breast cancer risk. Nonetheless the actual association is still debatable. Furthermore, estrogen is very crucial in maintaining human bone density and gradually decreases over age. A systematic search was conducted to assess any association of BMD with breast cancer risk factors among premenopausal and postmenopausal women. Materials and Methods: Review identification was performed through databases searching on MEDLINE, CINAHL and SCOPUS and 19 qualified studies were elected. The keywords used were "bone mineral density", "breast cancer", and "breast density". Results: A total of 19 articles showed variation with the majority of the studies focused on postmenopausal and a few focused on premenopausal women. Overall there was no concensus on effects. Conclusions: An enormous effort is being undertaken by researchers to prove that BMD might be one of the significant risk factors for breast cancer.

Keywords: Bone mineral density - breast density - breast cancer - premenopausal women - postmenopausal women

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Introduction

Breast cancer is well known to be one of the most common types of cancers among women from various backgrounds with incidence increasing with age. According to American Cancer Society, Cancer Facts and Figures 2016 it is estimated that in 2016, among US women there will be 246,660 new cases of invasive breast cancer and 40,450 breast cancer deaths. This analysis shows the number of women with risk of developing breast cancer is very high. In fact, more than 75% of all breast cancer occurs in postmenopausal women (Tremollieres, 2008).Therefore, the early detection of breast cancer is important in order to save the lives of these women.

Several risk factors were indicated to be the standard measure in detecting breast cancer. In addition, the risk factors for breast cancer are often prognostic factors (Zambetti and Tartter, 2013). The common risk factor related is diet including fruit and vegetables, alcohol, fibre, fat, soy isofflavones, lignans, tea and vitamin supplements (Qu et al., 2013). Besides, factors that increase the exposure of breast tissue to estrogens, such as older age at first birth, menopause, obesity, or post- menopausal hormone therapy, have been shown to be associated with increased risk of breast cancer (Kerlikowske et al., 2005).

Another commonly discussed risk factor is bone mineral density (BMD). Nonetheless, it is still uncertain whether it can be a strong risk factor of breast cancer. Breast cancer and osteoporosis have a major impact on quality of life and life expectancy, especially in postmenopausal women (Jemal et al., 2010). Breast cancer and osteoporosis commonly occur in postmenopausal women because it has a strong link with the reduction of estrogen level in postmenopausal women that leads to low bone calcium level. Estrogen has a central role in the maintenance of bone integrity. Its deficiency produces accelerated bone resorption leading to decreased bone mineral density (Fraenkel et al., 2013).

Even though, numbers of studies has been conducted to clarify this matter but there is no any significant result that could confirm it. To date, the relationship between BMD and particular causes of breast cancer, and whether this relationship depends on established common denominator factors (e.g., the estrogenic status), is still unclear (Tremollieres and Ribot, 2010). This clearly indicates that any associations of BMD with breast cancer risk and risk factors is still debatable. Therefore we conducted the present systematic review in order to analyse the mentioned association among the pre- and postmenopausal women.

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Materials and Methods

This systematic review was conducted according to 2009 PRISMA guidelines.

Search strategy

This systematic review was conducted to search for the studies on association of BMD with risk factors of breast cancer among premenopausal and postmenopausal women. A comprehensive literature search was done via MEDLINE, CINAHL and SCOPUS databases. The keyword used to perform the search included 'bone mineral density', 'breast cancer' and 'risk factor'. A flow diagram of the literature search strategy is shown in Figure 1.

Inclusion and exclusion criteria

The search was limited to journals published in English with BMD being one of the risk factors of breast cancer involving premenopausal and postmenopausal women as the subject population, from the year 2006 to 2015 were included whereas, studies that involved cancer treatment with post breast cancer assessment were excluded.

Quality assessment of included studies.

Focus on various methodological features was used to assess the quality of the reviewed study. The criteria were clearly defined inclusion criteria, the sample population, the objectives and the outcomes of the study. A scoring approach was not used to assess the quality of the study because the consensus on the quality of reviewed studies between the authors was met.

Data extraction

The data extraction method was done individually by two reviewers using PICOS technique where all the data extracted used to form a table (Table 1). However,

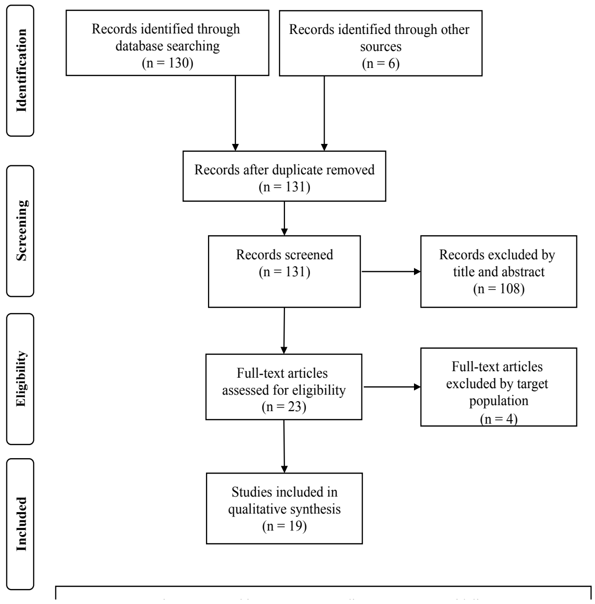

Figure 1. Searching strategy according to PRISMA guideline

Table 1. Summary of Articles Included in Review

NO	Author	Objectives	Study Design	Population	Statistical Analysis	Outcomes
1	Merav Fraenkel et al. 2013	To assess whether BMD is associated with risk of subsequent diagnosis of breast cancer in an unselected population of women.	Retrospective study	Women who had no prior diagnosis of breast cancer at the time BMD measurement (n= 14461)	T-test, ANOVA, Chi-square, Mann-Whitney U, Spearman rank, Kaplan-Meier survival analysis, log-rank test, Cox regression.	Positive correlation between BMD and breast cancer incidence in the population.
2	Zambetti, Tartter. 2013	To identify women with breast cancer and low bone mineral density will have lower breast cancer recur-rence rates than women with normal bone densities.	Not stated	Postmenopausal Caucasian women(N= 307)	t test, chi square	Bone mineral density is a significant prognostic factor for postmenopausal Caucasian women with breast cancer.
3	Melton et al. 2012	To estimate fracture risk among unselected community women with breast cancer and to systematically assess association with various risk factors including breast cancer treatments.	Cohort study	Women who resided in Olmsted County when first diagnosed with tissue-confirmed, invasive breast cancer in 1990-99(n=608)	log rank analysis.	Breast cancer patients in general are not at greatly increased fracture but neither are they protected from fractures despite any determinants that breast cancer and high bone density may have in common.
4	Conde et al. 2012	To compare the values of BMD in postmenopausal women with and without breast cancer.	Cross sectional	Breast cancer survivor women(n=51), women without breast cancer(n=71)	t test, Fisher's exact test, Uncon-ditional logistic re-gression analysis.	The prevalence of abnormal BMD was higher in postmenopausal breast cancer survivors than in postmenopausal women without breast cancer.
5	Sung et al. 2011	To examine the association between BMD and mammographic density.	Not stated	Female participants of the Healthy Twin study with both mammogram and BMD measurements obtained (n=730)	t test, chi-square, linear regression analysis	No significant genetic correlation between percent dense area the BMD at any site.

Table 1. (Continued) Summary of Articles Included in Review

NO	Author	Objectives	Study Design	Population	Statistical Analysis	Outcomes
6	Kalder et al. 2011	To examine the relationship between BMD measured by DXA and quantative ultrasonometry (QUS) in pre- as well as postmenopausal women with breast cancer compared to healthy matched controls.	Case-control study	Premenopausal (n=238) and premenopausal (n=1184) women.	Unpaired two-tailed t test, chi-square, mann-whitney U	Higher BMD irrespective of the method and site of measurement in postmenopausal women with breast cancer compared to control.
7	Debjani Grenier et al. 2010	To determine if higher bone density (BMD) is a risk factor for breast cancer in women age 50 years and older.	Not stated	Women aged 50 and above with no previous breast cancer history(n=37860)	chi-square	BMD in the lumbar spine in women > 50 year old is an independent risk factor for any breast cancer and ER-positive breast cancer.
8	Mann et al. 2009	To assess the prevalence of secondary causes of low bone density in patients with breast cancer.	Observational study	Female patients within 5 years of breast cancer diagnosis and age older than 50 years at diagnosis (n=200)	t test, Chi-square or Fisher's exact test.	Secondary causes of low BMD are common in postmenopausal women, especially those with endocrine-responsive breast cancer.
9	Yong et al. 2009	To assess the associations of breast cancer and bone densities with follicular phase hormones and sex hormone binding globulin (SHBG) in postmenopausal women.	Not stated	Women aged 40-45 year old (n=192)	Correlation analyses.	Associations were observed between breast and bone densities and serum hormone concentrations during follicular phase of menstrual cycle.
10	Chen et al. 2008	To estimate a woman's risk of breast cancer within a certain time period.	Prospective study.	Postmenopausal women who has baseline hip BMD and Gail score from the Women's Health Initiative were included. (n=9941)	ANOVA, Logistic regression analysis.	The contribution of BMD to the prediction of incident postmenopausal breast cancer across the entire population was found to be independent of the Gail score.
11	F.A Tremollieres. 2008	To investigate the relationship between BMD and the risk of breast cancer (BC) in perimenopausal and young postmenopausal women. To determine the contribution of BMD to breast cancer risk relative to other clinical breast cancer risk factors.	Prospective study	Perimenopausal and postmenopausal women (n=2137)	Chi-square Mann-Whitney	No relationship between BMD measured within the first menopausal and the risk of breast cancer.
12	Gupta et al. 2008	To evaluate the relationship between mammography breast density (MBD) and BMD.	Not stated.	Kuwaiti women (n=248)	Kruskal-Wallis test, One way ANOVA, Spearman's correlation.	No correlation between MBD and BMD was observed.
13	Crandall et al. 2007	To determine mammographic breast density and BMD are inversely associated in premenopausal women. To determine whether the association between BMD and mammographic density differs in premenopausal compared with perimenopausal women.	Cross sectional analysis.	Women aged 42 to 52 and premenopausal or early perimenopausal (n=3302)	Pearson and spearman correlation.	Mammographic breast density is inversely associated with BMD in the perimenopausal participants.
14	Cauley et al. 2006	To determine the contribution of BMD to breast cancer risk relative to other established breast cancer risk factors in postmenopausal women with osteoporosis.	Not stated	Women assigned to placebo in the MORE and CORE trials(N=2576), women participated in 4 years MORE trial(n=1290), women participated in the 8 years MORE plus CORE (n=1286)	Chi-square test, paired t-test.	BMD is a relatively weak predictor of breast cancer risk in these postmenopausal women with osteoporosis.

Table 1. (Continued) Summary of Articles Included in Review

NO	Author	Objectives	Study Design	Population	Statistical Analysis	Outcomes
15	Silverstein et al	To determine if BMD pre-screening is useful in selecting women for continued screening mammograms.	Case-control study	Women newly diagnosed with breast cancer(n=79), women with normal mammogram(n=158)	Paired t test, t tests, Conditional logistic regression	BMD is not useful as pre-screening predicator of mammography in older women and using it as such would result in cases of breast cancer being missed.
16	Kerlikowske et al	To determine whether mammographic breast density and BMD of the hip and spine are correlated and independently associated with breast cancer risk.	Cross sectional & nested case-control study	Cross sectional(N= 15254), Nested case control N=208(women with breast cancer), N=436(control subjects) among women aged 28 or older.	Chi-square test, multivariable logistic regression, Pearson's correlation, Spearman rank test, t test	Breast density is strongly associated with increased risk of breast cancer whereas BMD is not.
17	Stewart et al	To examine the relationship between BMD, bone loss and bone turnover with breast cancer risk in perimenopausal and younger age group.	Not stated	Women aged 45 to 54 years (n=5119)	t test or chi-square. Cox regression model.	In perimenopausal or early menopausal women there is no relationship between the incidence of breast cancer and BMD, change in BMD or bone turnover.
18	Crandall et al	To identify whether the association between mammographic breast density and bone mineral density would suggest a unifying mechanism influencing both breast density and BMD.	Cross sectional study	Women aged 45 to 65 years and atleast 1 year postmenopausal(n=875)	Multiple regression analyses.	Mammographic density and BMD are positively associated in women who have not recently used postmenopausal hormone.
19	Buist et al	To examine the cross sectional relationship between BMD and mammographic breast density is related to lifetime exposure to endogenous and exogenous estrogens.	Cross sectional	Postmenopausal women above age 54 (n= 1800)	Linear regression and Multivariate regression analysis.	BMD and breast density were not positively associated although both are independently association with estrogen exposure.

these studies have no intervention and comparator. Therefore, the intervention and comparator were ignored. The data extractions were done by taking few items into considerations. The items were the journal's title, the name of the first author, year of publication, objectives, study design and population, statistical analysis used, and outcomes. Dissimilarity regarding interpretation was determined by arbitration, and consensus was reached after discussion.

Discussion

There is no denying the fact that early detection of breast cancer can save lives. For this reason many risk factors of breast cancer are being identified to save the lives of many women out there who have the chances of getting breast cancer. Several risk factors for breast cancer have been identified including a history of breast cancer in first-degree relatives, obesity, smoking, early menarche, late menopause, hormone replacement therapy (HRT) and prolonged estrogen exposure. In current practice, mammogram remains the recommended screening method for the detection of breast cancer. In addition to this, ultrasound examination is also used particularly, in patients with dense breast for more detailed information. In our review many factors that could contribute to the increased risk of breast cancer are discussed as below:

Mammographic density is one of the strong risk factor of breast cancer. A potential mechanism for this association is the cumulative exposure to hormones that stimulate cell division in breast stroma and epithelium which may have corresponding effects on breast cancer development (Sung et al., 2011). Previous studies have suggested that women with high mammographic breast density (MBD) are at increased risk of breast cancer. Based on the study conducted by Kerlikowske in 2005 suggested that breast density is strongly associated with increased risk of breast cancer, even after taking into account reproductive and hormonal risk factors. Early menarche, late menopause, high BMI and postmenopausal hormone therapy (PHT) are all the indicators of estrogen exposure in a women's body (Tremollieres., 2008) and mammographic breast density is associated with some of the established risk factors for breast cancer being related to endogenous and exogenous estrogen (Sung et al.,2011). This demonstrates the strong association of estrogen exposure with high breast density and increased risk of breast cancer.

According to the National Breast Cancer Foundation, 2015, frequent consumption of alcohol can increase the risk for breast cancer. The more alcohol we consume, the greater the risk. In addition, alcohol consumption has been estimated to account for 5% of breast cancer incidence in the European Prospective Investigation into Cancer and Nutrition (EPIC) study (Schutze et al., 2011). Hong (2010) mentioned that alcohol increases circulating estrogen levels through interaction with estrogen metabolism for the reason that alcohol can alter the way a woman's body metabolizes estrogen hence, resulting in increased estrogen level. Consequently, estrogen levels are higher in women who drink alcohol than in non-drinkers (Key, 2011).

Poor exposure to physical activity is said to increase the risk for breast cancer evidenced in a prospective study by Eliassen (2015) which concluded that moderate physical activity, including brisk walking, may reduce postmenopausal breast cancer risk and that increases in activity after menopause may be beneficial. Besides, based on a meta-analysis study conducted by Wu et al (2013) they concluded that physical activity is significantly associated with reduced risk of breast cancer and physical activity should be advocated for the primary prevention of breast cancer. This is mainly because it provides many health benefits, including weight loss and maintenance, improved insulin sensitivity, and improved lipid profile (McTiernan., 2008). Physical activity such as a one-year aerobic exercise can help to reduce the chances of breast cancer by reducing body weight, total body fat, intrabdominal fat area and subcutaneous abdominal fat (Friedenreich et al., 2011) thus reducing body mass index (BMI) and chances of obesity. However, the effect of BMI to risk of breast cancer differs in women before menopause and after menopause. Prior menopause, being overweight or obese modestly decreases breast cancer risk (Nelson et al., 2012) and after menopause, being overweight or obese increases breast cancer risk (Reeves et al., 2007).

Majority of searched studies carried out on this issue discusses about the correlation of bone mineral density (BMD) with breast cancer risk factors among postmenopausal women, few discusses about its effect in premenopausal women. In an observational study, to assess the prevalence of secondary causes of low bone density in patients with breast cancer, the median age of all the women during diagnosis was 62 years (Mann et al., 2009). In the Rotterdam study, the women studied were all over the age of 55 years, with a mean age of 65.5 years (Van der Klift et al., 2003) while, in a prospective study to investigate whether hip BMD predicts postmenopausal breast cancer risk independently of the Gail score the sample used were postmenopausal women with an average age of 63.0 ± 7.4 years at baseline (Chen et al., 2008). This indicates that all the studies focuses more on postmenopausal or older aged women.

In contrast to all these studies, in a research conducted by Stewart in 2005 stated that perimenopausal women aged 45 to 54 years were selected as the study aims to examine the relationship between BMD, bone loss and bone turnover with breast cancer risk in premenopausal and younger age group. Besides, in MABOT II study both pre- and postmenopausal women were made as sample (Kalder et al., 2011). Equal emphasis is given to both groups of women as the hormone imbalance can take place at any age. This can be proven when women at the age of as early as 40 years old undergo premenopausal hormone therapy (PHT). As for the women in the postmenopausal age their estrogen level degrades and they will undergo hormone replacement therapy (HRT). Those with low baseline BMD were more likely to be on HRT (Stewart et al., 2005) as HRT or estrogen therapy functions to stabilise the estrogen level and helps regulate blood calcium level thus, preventing bone loss in estrogen-deficient women (Komulainen et al., 1998).

In addition, when a sample is taken for a study relating BMD and breast cancer age and HRT usage factor is given special observation as it influences the estrogen level in body. High HRT usage may be masking the results, since HRT is more likely to have been used in those with low BMD (Stewart et al., 2005). Usage of HRT in postmenopausal women increases estrogen level which may show an increased risk of breast cancer. It is reported in a study that HRT was not associated with an increased risk of breast cancer at any disease stage, regardless of duration or recency of use (Weiss et al., 2002) which indicates that HRT usage still not clear to rule out its effect on breast cancer risk. Meanwhile, there are few studies that discusses the effect of combined HRT (contains the hormone estrogen and progesterone) to breast cancer risk factors (Weiss et al., 2002)

Studies also carried out about the method of investigating the association of BMD and breast cancer which is using the traditional breast cancer risk assessment tool, the Gail score. The Gail risk model is a well- known tool that estimates the 5-year and lifetime risk of invasive breast cancer for women aged ≥35 years (Gail et al., 1989). However, not many studies have discussed about this. The correlations among BMD, traditional breast cancer risk assessment tool results (such as the Gail risk model), and breast cancer incidence have not yet been examined (Chen et al., 2008). To our knowledge there is only one study by Chen et al that discusses about this, where they investigated about whether hip BMD predicts postmenopausal breast cancer risk independently of the Gail score and it is concluded that using both BMD and Gail score together may improve the performance of the prediction model with regard to incident breast cancer in postmenopausal women, but the gain in the accuracy of the prediction is small.

In conclusion, in reference to all the articles indicates that immense effort is being taken by many researches to prove that BMD might be one of the positive and significant risks of breast cancer. Other risk factors that have been discussed above also plays an important role in regulating the estrogen level that can be a major indicator to breast cancer risk factors. Several harmful factors related to diet, lifestyle or the surrounding environment affects or determines the quality of life. It is possible that these differences are partly responsible for the regional disparities observed in breast cancer incidence.

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