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Review of: Are breast density and bone mineral density independent risk factors for breast cancer?

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K. Kerlikowske, J. Shepherd, J. Creasman, J. A. Tice, E. Ziv, S. R. Cummings. Are breast density and bone mineral density independent risk factors for breast cancer. ***Journal of the National Cancer Institute*** 2005; **97**(7): 368–74.

Abstract of the original article
Background: Mammographic breast density and bone mineral density (BMD) are markers of cumulative exposure to estrogen. Previous studies have suggested that women with high mammographic breast density or high BMD are at increased risk of breast cancer. We determined whether mammographic breast density and BMD of the hip and spine are correlated and independently associated with breast cancer risk. *Methods:* We conducted a cross-sectional study ($N = 15\,254$) and a nested case-control study (of 208 women with breast cancer and 436 control subjects) among women aged 28 years or older who had a screening mammography examination and hip BMD measurement within 2 years. Breast density for 3105 of the women was classified using the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) categories, and percentage mammographic breast density among the case patients and control subjects was quantified with a computer-based threshold method. Spearman rank partial correlation coefficient and Pearson's correlation coefficient were used to examine correlations between BI-RADS breast density and BMD and between percentage mammographic breast density and BMD, respectively, in women without breast cancer. Logistic regression was used to examine the association of breast cancer with percentage mammographic breast density and BMD. All statistical tests were two-sided. *Results:* Neither BI-RADS breast density nor percentage breast density was correlated with hip or spine BMD (correlation coefficient $= -.02$ and $-.01$ for BI-RADS, respectively, and $-.06$ and .01 for percentage breast density, respectively). Neither hip BMD nor spine BMD had a statistically significant relationship with breast cancer risk. Women with breast density in the highest sextile had an approximately threefold increased risk of breast cancer compared with women in the lowest sextile (odds ratio: 2.7; 95% confidence interval: 1.4–5.4); adjusting for hip or spine BMD did not change the association between breast density and breast cancer risk. *Conclusion:* Breast density is strongly associated with increased risk of breast cancer, even after taking into account reproductive and hormonal risk factors, whereas BMD, although a possible marker of lifetime exposure to estrogen, is not. Thus, a component of breast density that is independent of estrogen-mediated effects may contribute to breast cancer risk.

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Review

In this modern era of publish-or-perish, in which researchers so often dredge their data sets to 'find a story' before publishing what ultimately turns out to be a false positive finding, it is reassuring to read the recent publication by Kerlikowske and colleagues [1]. They found that breast density as measured by mammography, and bone (mineral) density as measured by dual energy X-ray absorptiometry, were not correlated. They also found that bone density was not a risk factor for breast cancer.

The correlation coefficients between different measures of breast density and bone density at different sites and in different subgroups, before and after adjusting for different sets of covariates, were all in the range −0.11 to 0.09 (Table 4). Given that the number of subjects overall was more than 2000, the (unreported) standard error of the overall correlation estimate is approximately 0.02 and the study had 80% power to detect effects outside the range of −0.05 to 0.05 at the $P = 0.05$ level of significance. Therefore, if there really is an association between breast density and bone density, its overall magnitude is minimal. This definitive null finding has profound implications; it illustrates how little we know about the causes of variation in breast density (see below), and suggests that its effects on breast cancer risk may not be related to estrogen-mediated factors [1].

Breast (or mammographic) density is the area of the two-dimensional representation of the breast on a mammogram that appears radiographically dense, and is presumed to represent connective and epithelial breast tissue. The percentage of a mature woman's breast that is mammographically dense is, on average, about 30–40% and declines slowly with age and after menopause when non-dense area increases. It differs widely across the population at all ages; the standard error of percentage breast density adjusted for age and body mass index is about 10–15 percentage units. It is a well-established and strong risk factor for breast cancer, independent of age and other risk factors measured by questionnaires [2].

Bone (mineral) density is a two-dimensional measure of the attenuation of a weak X-ray beam through the body and is correlated with the amount of calcium in the bones. It is a well-established risk factor for osteoporotic fractures [3].

Both breast density and bone density have generally been considered to reflect the cumulative effects of estrogen [1]. For example, breast density can be changed by interventions involving hormones [4–6] and tamoxifen [7], while reproductive factors which affect exposure to endogenous estrogen and progesterone are associated with age-adjusted breast density [8]. Estrogen plays an important part in the regulation of bone turnover, and the determination of peak bone density and age-related loss of bone density [9]. It has therefore been hypothesized that these two disease biomarkers could be associated with one another [1].

The idea that breast density and bone density may be correlated was also given indirect empirical support by the Study of Osteoporotic Fractures [10]. This claimed to have shown that women in the highest quartile of bone density at the distal radius or metacarpal had a two- to three-fold increased risk of breast cancer. Some subsequent studies claimed to confirm this association, other published studies did not, and one wonders how many other negative studies are as yet unpublished. Kerlikowske and colleagues [1] found no evidence that bone density was a risk factor for breast cancer.

The hypothesis above is one we also thought was worth pursuing. Twin and family studies have shown that the majority of variation across the population, in both breast density and bone density, is likely due to genetic factors. We wondered if the same genes that explained so much of the wide variation in breast density were also involved in explaining the genetic variation of bone density, and if so, whether these might be genes involved with estrogen metabolism. To do so we conducted a study of 134 female twin pairs [11], and were so surprised by our finding of no association that we delayed writing it up while completing other work. In the meantime, Kerlikowske and colleagues published their null results [1].

Our twin study confirmed that there is no appreciable association between breast density and bone density, at either the forearm, femoral neck or lumbar spine [11]. We found the correlations between breast density and bone density measures within the same individual were close to zero and none were nominally statistically significant. The same applied to the correlations between breast density in one twin and bone density in the other twin; none were significant. Had the same genetic factors been implicated in both traits, we would have expected these 'cross-trait cross-twin correlations' to be significantly greater in monozygotic pairs than in dizygotic pairs. We therefore concluded that there is little, if any, overlap between the genetic, or environmental, determinants of disease risk associated with these traits.

The absence of any correlation between breast density and bone density may be due to the manner in which they are affected by estrogen exposure. For example, bone density appears to be related to cumulative estrogen exposure whereas increases in mammographic density seem to occur during the luteal phase of the menstrual cycle.

Perhaps the most important implication of these two studies is that they demonstrate that estrogens

might explain little variation in breast density. Given the current wisdom that estrogens are major risk factors for breast cancer, the evidence relating *albeit* small changes in breast density to differing levels of estrogens and other hormones has generally been driving some thinking. It is important to note, however, that these hormone-related factors (as currently measured) explain only a small proportion of the wide population variation in breast density [2]. Weight or body mass index are associated with percentage breast density, and with mammographically non-dense area, but have little relationship to mammographically dense area [12,13]. Age is weakly associated with breast density measures. After adjusting for age and body composition, other measured determinants explain at most a few percent of the variance of the breast density measures above (see e.g. [14] Appendix).

Our previous twin study [14] showed that the majority of the variance of breast density, after adjusting for measured factors that influence mean levels, appears to be explained by genetic factors. The correlation in breast density within monozygotic pairs was about 0.6, significantly greater than the correlation within dizygotic pairs of about 0.2–0.3. The same results were observed in large samples from both Australia and North America. These results apply to percentage breast density [14], and to dense breast area and non-dense breast area [12,13]. Under the assumptions of the classic twin model, we concluded that about 60% of the adjusted variance of these breast density measures was due to as yet unmeasured genetic factors, and there was no evidence of environmental factors shared by twins having an effect on breast density in mid-life. We are now studying sister pairs, including the sisters of twins, to see if non-twin sisters are as correlated as dizygotic pairs and so determine whether there are shared environment affects specific to twin pairs.

So what are the genetic determinants of breast density, and how can they be found? Our new twin study suggests that the genes that explain the genetic variance of breast density are not the same as those that explain the genetic variance of bone density. There has been much written about the genetic determinants of bone density, but little if any population variance can be definitively apportioned to variants in any specific gene.

Boyd and colleagues [2] discuss several ways one might go about finding the genetic determinants of breast density. These include candidate gene studies and genome wide scans using, for example, sister pairs extremely concordant or extremely discordant for breast density measures. We and others are now pursuing these strategies. The identification of genetic loci associated with variations in breast density may lead to the identification of new genes associated with differences in susceptibility to breast cancer, provide insights into the biology of the breast, and identify potential targets for prevention.

In conclusion, little of the wide population variance in breast density is explained by known measured factors after adjusting for age and body size. Breast density adjusted for age is a strong predictor of breast cancer, independent of other known risk factors for the disease. The causes of variation in breast density are not the same as those for bone density. If one is to believe that estrogen plays an important role in determining variation of bone density in mid-life, and the most compelling evidence of this is the rapid fall in bone density around and immediately after the menopause [9], then one would have to argue that estrogen levels, and therefore genes involved in estrogen metabolism, may explain little if any variation in breast density. This does not necessarily argue against studies of variants in hormone metabolisms genes, because there is nothing quite as compelling as empirical direct evidence. It does suggest, however, that a much wider view of the genetic – and for that matter non-genetic – causes of variation in breast density, and hence risk of breast cancer, is required.

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