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

J. L. Hopper
Centrefor Molecular, Environmental, Genetic and Analytic Epidemiology, The University of Melbourne, Carlton, Vic., Australia.

Citation of original article:

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 = 15254) 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.
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, how-
ever, that these hormone-related factors (as cur-
cently measured) explain only a small proportion of
the wide population variation in breast density [2].
Weight or body mass index are associated with per-
centage breast density, and with mammographically
non-dense area, but have little relationship to mam-
ographically dense area [12,13]. Age is weakly asso-
ciated with breast density measures. After adjusting
for age and body composition, other measured deter-
minants explain at most a few percent of the vari-
ance of the breast density measures above (see e.g.

Our previous twin study [14] showed that the major-
ity of the variance of breast density, after adjusting
for measured factors that influence mean levels,
appears to be explained by genetic factors. The cor-
relation in breast density within monozygotic pairs
was about 0.6, significantly greater than the correla-
tion 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 con-
cluded that about 60% of the adjusted variance of
these breast density measures was due to as yet
unmeasured genetic factors, and there was no evi-
dence of environmental factors shared by twins hav-
ing 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 vari-
ance in breast density is explained by known mea-
sured 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 immedi-
ately 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 neces-
sarily 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.

Acknowledgments

National Health and Medical Research Council
(Australia), Victorian Breast Cancer Research
Consortium.

References

breast density and bone mineral density independent
97: 368–374.

density as an intermediate and heritable phenotype for

BMD for hip and other fractures. J Bone Miner Res 2005;
20: 1185–1194.

4. Layla MB, Gallagher JC, Schreiman JS, et al. Effect of
postmenopausal hormone replacement therapy on
mammographic density and parenchymal pattern.

study of increased mammographic density response to
hormone replacement therapy. Cancer Epidemiol Biomark

pausal hormone therapy and change in mam-

7. Cuzick J, Warwick J, Pinney E, et al. Tamoxifen and
breast density in women at increased risk of breast can-