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# Mammographic density as a predictor of breast cancer outcome

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## Summary

This clinical investigation explored mammographic density, a strong etiologic risk factor for breast cancer, as a predictor of local breast cancer recurrence. The authors reported that women with intermediate and high breast density had a significantly elevated risk to develop a local breast cancer recurrence. However, this effect was only observed among patients who had not received radiotherapy. Only two previous reports have shown that mammographic density may be a prognostic factor, but the studies disagree on the role of radiotherapy as an effect modifier. Future studies that incorporate additional risk factors, e.g., obesity, need to examine the role of mammographic density in larger patient population before including breast density in treatment decision models.

### Keywords

Breast cancer; mammographic density; recurrence; tissue; risk prediction

## Summary of methods and results

The paper under discussion is one of the first to examine mammographic density as a prognostic rather than an etiologic factor [1]. Breast density, one of the strongest breast cancer risk factors, refers to the radiographic appearance of the female breast [2,3]. Fat, which is radiolucent, appears dark on a mammogram. Epithelial and fibrous stromal tissues, on the other hand, appear white or radiodense and are collectively referred to as mammographic density. Relative to a low percentage, a high percentage of radiological density confers a 4–6 fold risk for breast cancer [4]. Mammographic density is inversely associated with age and body weight and can be measured with qualitative and quantitative methods [4]. In this clinical study [1], 355 women with invasive breast cancer and pre-treatment mammograms were studied. All women had received breast-conserving surgery and 235 of them also underwent radiotherapy. Information about local recurrence was obtained from medical records and mammographic images were classified into low, intermediate, and high density by two radiologists using a qualitative classification scheme. The respective proportion of recurrences for the three density groups were 3/99, 11/107, and 20/129. Cox proportional hazards models indicated that women with intermediate and high mammographic density were 3.6 and 5.7 times more likely to develop local disease recurrence than women with low density, whereas there was no difference between the two groups in the rate of distant disease recurrence. A subgroup analysis showed that this difference was limited to women who had not received radiotherapy; for patients who had received radiotherapy, breast density was not a predictor of local recurrence. The authors discussed that women in different arms of clinical trials should be balanced with respect to

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mammographic density and raised the question of mammographic density as a potentially useful marker to select breast cancer patients who should receive radiotherapy.

## Discussion

The choice of breast cancer treatment to yield the optimal outcome with minimal adverse effects has become a major issue as more and more aggressive treatment regimens have been developed [5]. This clinical study is proposing an innovative approach to select the appropriate treatment [1]. However, the conclusions need to interpreted with caution because the cases in this report were diagnosed in 1987–1998 when treatment guidelines were different from the current recommendation to offer radiotherapy to the majority of patients treated with breast-conserving surgery [6]. The study was also limited by its relatively small sample size and the lack of information on body weight. In addition, a computer-assisted density assessment method as used in most epidemiologic investigations would have been desirable [4].

The available literature to evaluate mammographic density as a prognostic factor is very limited [7–10]. Preoperative mammographic features, such as calcifications, were shown to be useful to identify patients at risk of local recurrence and to help select patients who may be unsuitable for breast-conserving surgery, but the findings were not considered sufficient evidence for withholding of radiotherapy outside the context of clinical trials [8,9]. Among women with ductal carcinoma in situ, those with highly dense breasts were at substantially higher risk for a second breast cancer than women with less dense breast even after taking radiotherapy into account [7]. Only one small nested case-control study among 136 women examined local recurrence as an endpoint in relation to breast density and showed that women in the highest breast density category had a 4-fold higher risk for local recurrence than those in the lowest category [10]. The three studies did not agree whether radiotherapy modified the association of mammographic density with recurrence [1,7,10]. Whereas Cil et al. observed an effect in women not having radiotherapy only [1], an increased risk was seen in the Park et al. study whose participants had all received radiotherapy [10]. In contrast, mammographic density predicted recurrence after in situ cancer in women treated with and without radiotherapy [7].

In contrast to Cil et al. [1], body mass index (BMI) was included in the models by Park et al. [10]. Obesity was found to be a stronger predictor of local recurrence than breast density. Among 11 obese women, 6 experienced a local recurrence. Although the small sample size warrants caution [10], these findings raise the question how controlling for BMI might have affected the findings by Cil et al. [1]. Breast density decreases with BMI due to its strong correlation with the non-dense (fatty) area on the mammogram. In etiologic research, BMI is a negative confounder of the association between mammographic density and breast cancer risk because it has an inverse association with the former and a direct association with the latter. Given that obesity has been found to be associated with poorer breast cancer outcomes in many studies although survival and not local recurrence was the endpoint in most reports [11–13], including BMI as a covariate would likely strengthen the association between mammographic density and recurrence. This idea is supported by observations made in the two previous studies of mammographic density and prognosis [8,11]. Therefore, a decision about radiotherapy after breast-conserving surgery should consider BMI.

The question of a biological mechanism for the positive association of mammographic density with breast cancer development and progression remains of great interest. The dense areas seen on mammograms may represent connective tissues, such as Cooper's ligaments, interlobular fibrous tissue, periductal fibrosis, and intralobular fibrous tissue surrounding the glandular tissue [14]. Semi-quantitative and quantitative microscopy has demonstrated that after adjusting for age, mammographic density is associated with glandular area, the number of both epithelial and non-epithelial cells, and the amount of collagen [15–19]. Percent dense area is related to higher fibrosis [16,20] and among biopsied populations, with epithelial hyperplasia [21]. The amount of connective tissue is far greater (~11-fold) than glandular tissue [22] and contributes more to the variability in percent dense area [15–17,21]. It has been speculated that the collagen density associated with mammographic density itself can enhance tumor formation through epithelial-stromal interactions [23,24] or that mammographic density simply represents the number of cells at risk, thereby increasing the probability of a malignant transformation [19].

A small number of immunohistochemical studies have been performed to understand how these tissue characteristics may be involved in carcinogenesis. Markers of cell proliferation [19,25, 26] and the expression of sex hormone receptors [18,25,27] have shown relatively little association with mammographic density. Growing evidence supports the notion that altered regulation of extracellular matrix (ECM) contributes to neoplastic progression and that disruptions in the ECM may precede epithelial changes [28]. Thus, matrix metalloproteinases (MMPs), endopeptidases involved in remodeling of ECM, could play a role [29]. In the only published report, no association between MMP-1 and 12 expression in breast tissue and mammographic density was detected [30], but weak associations with the expression of tissue inhibitor of metalloproteinases (TIMP)-3 were observed in two investigations [15,30].

As a way to connect stromal properties and prognosis, it can be hypothesized that cancer is a response to an abnormal stromal environment. The aberrant stroma may predispose tissue to cancer by accelerating the progression of initiated cells [31] and, in the case of recurrence, the local tissue microenvironment may remain permissive for regrowth [32]. Transforming growth factor (TGF)-β could be one molecular mechanism mediating the stromal-epithelial interaction given its role in mammary carcinogenesis [32]. Interestingly, the only gene expression study reported to date observed lower TGF-β signaling in dense than non-dense breast tissue [27]. Future gene expression studies will need to shed light on the pathways involved in the accumulation of dense tissue and its effects on carcinogenesis and recurrence [27].

## Future perspective

In parallel with a possible role in prognosis, breast density has been found to be useful for breast cancer risk prediction [33]. As a method to identify high-risk subjects for prevention efforts, a model to predict individualized probabilities of developing breast cancer, the Gail model [34], is commonly applied despite its modest discriminatory accuracy. Adding breast density to the model improves its discriminatory accuracy; the *c*-statistics ranged between 0.62–0.66 in models with breast density as compared to 0.58–0.63 in those without [33]. If the findings by Cil et al. can be replicated [1], models for treatment decisions may also benefit from including mammographic density although radiotherapy will usually be offered under the current recommendations [6]. Given the wide availability of prediagnostic mammograms, it would be feasible to reanalyze breast cancer clinical trials for differences in outcomes according to breast density or to include breast density measurements in future clinical trials. There is no reason why density assessment should be limited to the question of radiotherapy, but the characteristics of highly dense breast tissue constitute a biologic reason to think that radiotherapy would have a more pronounced effect on stroma and ECM that constitute mammographic density than would other treatment modalities. For future studies, it may be useful to examine if mammographic density changes with radiotherapy; this intermediate effect may occur because radiotherapy induces fibrosis in certain cases [35]. If radiotherapy is affecting the ECM such that it does not support recurrence, there may also be drugs to target the ECM [36]. Finally, research efforts are already underway to assess the possible impact of breast density on breast cancer survival.

# Executive summary

## Study design

- Retrospective medical records review among women with breast-conserving surgery for invasive breast cancer diagnosed in 1987–1998.
- Classification of pretreatment mammograms into low, intermediate, and high mammographic density.
- Local disease recurrence after 1–15 years was considered the endpoint.
- Statistical analysis by Cox proportional hazards model with adjustment for confounders.

## Results

- The multivariate hazard ratios for local breast cancer recurrence were 3.6 and 5.7 for women with intermediate and high density as compared to those with low density.
- Mammographic density only affected local disease recurrence among patient who were not treated with radiotherapy.

## Conclusion

- Mammographic breast density appears to be a predictor for local breast cancer recurrence, in particular among women who did not receive radiotherapy.

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