Basic Physics and Doubts about Relationship between Mammographically Determined Tissue Density and Breast Cancer Risk

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Numerous studies have suggested a link between breast tissue patterns, as defined with mammography, and risk for breast cancer. There may be a relationship, but the author believes all of these studies have methodological flaws. It is impossible, with the parameters used in these studies, to accurately measure the percentage of tissues by volume when two-dimensional x-ray mammographic images are used. Without exposure values, half-value layer information, and knowledge of the compressed thickness of the breast, an accurate volume of tissue cannot be calculated. The great variability in positioning the breast for a mammogram is also an uncontrollable factor in measuring tissue density. Computerized segmentation algorithms can accurately assess the percentage of the x-ray image that is “dense,” but this does not accurately measure the true volume of tissue. Since the percentage of dense tissue is ultimately measured in relation to the complete volume of the breast, defining the true boundaries of the breast is also a problem. Studies that purport to show small percentage differences between groups are likely inaccurate. Future investigations need to use three-dimensional information.

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There is a broad spectrum of breast tissue patterns as demonstrated with mammography. There has long been an interest in understanding these patterns (1–13), measuring them, and linking them to an individual’s risk for developing breast cancer. The authors of several recent articles (14–16) attempt to reinforce the belief that tissue density, as derived from x-ray mammograms, is a major risk factor for breast cancer—perhaps the strongest risk factor (17). Although I personally suspect that there is a relationship between density and risk, the degree is far from clear, since I believe the studies that have been published provide analyses that go beyond what is physically possible in terms of accurately measuring the percentage volume of breast tissue that is dense. Furthermore, “dense” tissues are not homogeneous but are composed of fibrous connective tissue, ducts, and lobules in various percentages. The relative percentages of these components are presently not measurable on two-dimensional (2D) mammographic images. Consequently, it is unclear which tissue compartment, if any, is related to breast cancer risk. Modern computer segmentation techniques that can measure the percentage of light gray to white areas (fibroglandular tissue) portrayed on the mammogram relative to the amount of dark gray to black areas (predominantly fat) on the image are no doubt highly reproducible (18). However, the true accuracy of the measurements in terms of a direct relationship to the absolute volumes of these tissues has never been shown. The reproducibility of inaccurate measurements does not establish scientific validity.

Basic physics shows that the methods used to quantify the percentage of breast tissue that is dense cannot possibly measure the true volume ratio of dense to fatty tissue with any degree of accuracy, which casts doubt on virtually all published analyses. Without detailed exposure information—including information concerning the compressed thickness of the breast, as well as the quality of the x-ray beam used—and an understanding of the way the breast was positioned, it is scientifically impossible (not merely difficult, but impossible, in my opinion) to accurately measure the percentage of tissue volume that is dense on the basis of two-view mammograms. Since it is impossible, without additional information, to measure tissue percentages by using two projections, it is certainly impossible to accurately measure the percentage of dense tissue from a single mammographic projection. Publications that purport to have found single-digit percentage differences between breasts are reporting accuracies that I believe cannot possibly be achieved from the data that were used (19,20). Authors and reviewers alike have confused the ability to measure film blackening on a mammogram with the accuracy of measuring the true percentages of tissue volume that created those densities. Mammograms can be measured very precisely, but there are no data to support these measurements as accurate reflections of true volume ratios of the tissues. In my opinion, it is a failure of the peer review process that has permitted the publication of these articles and the perpetuation of this misinformation to achieve a status that is not supported by the science.

In the 1960s, Wolfe first suggested that tissue patterns, as defined with mammography, might be related to subsequent risk for the development of breast cancer (6,21). In the 1970s, interest increased and studies were performed to try to define the relationship (1,3,7). In 1984, Boyd et al (22) reviewed those studies and concluded that most suffered from methodological problems. They concluded that there was some increased risk associated with dense breast tissue but that its magnitude was fairly low. Radiologists lost interest in the relationship, since it was not of any practical value in advising women. There were still many women who developed breast cancer who had “fatty” breast tissue, and the relationships were not sufficiently strong enough to be used to tailor screening recommendations.

Radiologists became more concerned about the fact that dense breast tissue could obscure a lesion at mammography (23), and, consequently, the American College of Radiology developed a rating system based on Wolfe’s original four categories (6,21). These have been included in the American College of Radiology Breast Imaging Reporting and Data System, not as a means for establishing risks for developing breast cancer but as a way to alert referring physicians as to the likelihood that a cancer might be hidden on a mammogram.

In my experience, few radiologists have interest in tissue patterns as a marker of risk. Nevertheless, there has been a great deal of interest in the epidemiology community concerning tissue density and risk. Boyd continued his analyses, and, in 1992 he and colleagues published an article that suggested that women with dense breasts had five to nine times the risk of developing breast cancer, compared with those with fatty breasts (9). As was stated, this made tissue pattern one of the highest risks for breast cancer. Numerous articles have been written on the association, and most authors have concluded that there is some relationship between dense breast tissue and risk for breast cancer.

Most of the early studies of tissue pattern and cancer risk are based on the radiologist’s subjective assessment of patterns by using both mediolateral oblique (MLO) and craniocaudal (CC) projections. By using both projections, the radiologist has some nonquantitative information about the three-dimensional (3D) distribution of the denser tissues. This is, nevertheless, a subjective assessment, and reader variability is a clear problem in such analyses (24). There is also a simple geometric problem. Radiologists can “guesstimate” the percentage of breast tissue...
tissue that is dense, but they are still using 2D information to assess a 3D phenomenon, and they cannot possibly be accurate in any absolute sense. For example, a shell of dense tissue with fat on the inside (Fig 1) would have the same appearance to a radiologist looking from side to side (ie, MLO) and from top to bottom (ie, CC) of the breast as it would if the shell was full of dense tissue, yet the true percentage of dense tissue would be dramatically different.

To try to reduce the subjectivity associated with assessing and comparing tissue densities, efforts have been made to use computers to gauge the relative percentages of fatty and fibroglandular density on the mammogram (19). Screen-film mammograms have been digitized, and algorithms have been developed that can outline the portions of the image that represent dense tissues (segmentation). By knowing the area of dense tissue and the area of the entire breast from the skin to the edge of the mammogram, a ratio can be derived. Repeat measurements of the same images show that the results can be highly reproducible.

Unfortunately, reproducibility of objective measurements does not mean accuracy. In fact, it is a simple matter to show that the use of 2D mammograms alone to assess the ratio of dense to fatty tissue in the breast is inaccurate for determining the volume ratios of the tissues. The problem is that, without the important pieces of information noted earlier, which have been lacking in all the studies, it is not possible to determine the 3D volume ratio of dense to fatty tissue from a single 2D image. A simple way to understand the problem is by standing on the street looking at a hedge along the edge of a piece of property. It is impossible to determine from that single perspective how deep the hedge is. It would not be possible to know whether the hedge is a single row of plants or 20 rows deep. Similarly, it is mathematically impossible, without more detailed information, to extrapolate three dimensions from 2D information on a mammogram. If the hedge wrapped around the corner and the viewer looked from an orthogonal position (such as a second mammographic view) the viewer could still not determine whether the hedge was one row deep, scattered trees, or a full forest. The mammography problem is compounded by the fact that the breast is also distorted between the two projections due to mammographic compression.

Further compounding the problem with many studies is the fact that they have been performed using only the CC image to avoid having to deal with the density caused by the pectoralis major muscle, which is superimposed on the image on the MLO projection. This further reduces the value of the measurements because most CC projections miss large volumes of the breast. The example in Figure 2 clearly demonstrates how the measurement changes simply by repositioning the breast. A CC image was obtained (Fig 2a), but the

**Figure 1**

![Figure 1](image)

Figure 1: True volume of dense tissue cannot be accurately measured on 2D images without information on exposure values and breast thickness. Breast appears moderately dense on (a) MLO and (b) CC mammographic projections. (c) On transverse T2-weighted magnetic resonance (MR) image (repetition time, 5000 msec; echo time, 105 msec), fibroglandular tissue ("black" tissue) actually forms a shell around fat ("white" tissue) in center of right breast, and the breast is predominantly fat.
skilled technologist realized that she had not positioned the breast as far into the mammography device as she could, and she immediately repeated the mammogram and included more breast tissue in the field of view (Fig 2b). Simple observation shows that the percentage of fatty tissue is greatly increased by pulling the breast further into the machine. By segmenting the two images with a computer algorithm, the first image suggested that the breast was 27.6% dense tissue. However, by merely pulling the breast further into the machine more fatty tissue was revealed at the back of the breast, which reduced the percentage of dense tissue by half, to 13.0%. If repositioning the breast on the same day results in such inaccuracy, positioning the breast at another time is unlikely to be more accurate.

It will, no doubt, be argued that these are systematic problems that apply to all images and all participants in a study, so that even if absolute volumes cannot be compared the ratios can still be compared, given large enough numbers. If there were no other variables this might be true. However, the breast is not a block of material. The breast is a repository for fat. When a woman gains or loses weight, it is frequently reflected in the composition of her breasts. Changes in body weight can have a considerable effect on the percentage of dense breast tissue, and patient weight may not be the same when comparing two groups of women. If, for example, tissue patterns among women using hormones are compared with the patterns among those not using hormones, there may be other factors that influence the appearance of the breast on a mammogram and influence the measurements of one group compared with those of the other. There may well be differences in weight gain between women using hormones, which can influence breast tissue densities.

Another factor in trying to compare mammograms and percentage density lies in the method of obtaining mammograms. The breast must be pulled as far into the x-ray device as possible, and the breast is compressed to spread the tissue structures. There is a wide range of discomfort that women experience when having their breasts positioned and compressed for mammograms. This affects the amount of compression that can be used and how far into the x-ray device the breast can be pulled, all influencing the appearance of the proportions of tissues. In one study, for example, it was determined that the use of hormone therapy increased tissue density by 6% per year (18). This is far greater accuracy, in my opinion, than can be achieved given the measurement problems described above. Furthermore, it is entirely possible that women using hormones have more tender breasts, owing to edema, and do not permit full compression and will not allow themselves to be pulled as far into the device as possible. This could easily make their breasts appear to have become more dense (less compression), and the percentage of dense tissue would appear to be increased, while the same problems would not affect women not using hormones. This could influence the comparison of tissue density between two groups.

Another variable among premenopausal women is the phase of the menstrual cycle. It is likely that this affects tissue density owing to prevention of breast compression when the breast is sore (25). Thus, it cannot legitimately be argued that the problem is systematic and of no consequence.

The fundamental problem lies in the effort to extract 3D information from 2D images. This can be easily appreciated in the following example. Assume a series of 27 clear glass blocks assembled into a pile that is three blocks by three blocks by three blocks (Fig 3a). If you look down on the assembly it would not be possible to tell how many blocks were piled up (similar to total breast volume). This is the same as looking at a single mammographic projection (eg, CC projection). If we replace three of
Glass blocks can be used to understand why accurate measures of dense tissue cannot be derived from 2D images without other information. (a) Schematic shows 27 clear glass blocks. When viewed from top, it is impossible to know if there are only nine blocks or if there are more. (b) If three blocks are made of smoked glass, then the observer looking from the top could suspect that three of nine (33%) are smoked glass, when in fact three of 27 (11%) are actually smoked. (c) If three smoked glass blocks are stacked one on top of the other and viewed from the top, observer could surmise that one of nine (11%) are smoked but would have no way of differentiating this from one of 27.

The clear blocks with three that are made of smoked glass and position these blocks in a row (Fig 3b), we would be unable to know by just looking from the top what the actual percentage of smoked blocks is. Again this would be similar to a CC projection. If we assume that we are seeing all the blocks and that there are only nine, we might assume that the percentage of dense blocks was three of nine (33%) when, in fact, it actually is three of 27 (11%). In fact, since there is no way of telling how many layers of clear blocks there are, we cannot determine what percentage of the total blocks are smoked glass. If we arranged the blocks so that the smoked blocks are stacked on top of one another (Fig 3c), it would be impossible to tell (without some way of gauging absolute density) whether or not there are one, two, or three blocks (or more) that are made of smoked glass. Thus the proportion of smoked glass blocks could be one, two, or three of 27 or one of nine, and there is no way to tell which is the correct percentage. In fact, since we have no way of telling how deep the pile of blocks is, we could not possibly determine what percentage of the total volume of blocks is smoked glass. This is precisely the problem that one has in trying to estimate volumetric tissue density from a 2D mammogram. Even if we were able to look at the pile from the side (MLO projection), it would not be possible to determine whether we were looking at two planes of blocks with nine on a side for a total of 15 or a full pile of 27.

The problem is complicated in mammography because the breast is compressed and structures are stretched. Dense tissue may line up in a column on the CC view on one mammogram, but when the breast is compressed at another time the tissues might be inadvertently rolled by the technologist so that the percentage of tissue density appears to increase when the effect is merely an artifact of positioning. This would be similar to the smoked glass blocks being distributed on a diagonal.

In my opinion, these basic facts of physics render all of the studies published to date, which are based on mammographic images, applicable only for gross comparisons. Investigators who are interested in exploring tissue density and breast cancer risk need to start fresh and think three dimensionally. Single projection images could be used to estimate the volume of density if the x-ray exposure factors had been provided, the thickness of the breast had been recorded, and the half-value layers had been measured with a step wedge exposed in the images to permit density quantification. I am unaware of any studies having this information. The only way to assess 3D density objectively is with 3D data. Investigators should cease drawing conclusions based on 2D images.

Three-dimensional imaging information, such as that obtained with computed tomography, MR imaging (26), or digital breast tomosynthesis (27), can provide true volumetric information. However, even these 3D techniques are not without problems. To determine what percentage of the breast is dense tissue one must be able to identify not only what is dense tissue but also what constitutes the denominator of the ratio—namely, the total volume of the breast. This means that investigators will also need to decide where the breast actually ends, and I suspect that there is no agreement that can be reached to standardize that measurement.

There are major questions about the relationship between tissue density and risk, even if the reported observations about tissue volumes are accurate. For example, the percentage of women with dense breast tissues increases with decreasing age, yet breast cancer risk decreases with decreasing age. Lactating women have extremely dense breasts, yet breast cancer is rare among lactating women. Some may argue that it is the length of time that a woman has dense breast tissue that relates to her risk. If this is the case, then the data need to be stratified by age once accurate measures of tissue density can be developed. Much more comprehensive histopathologic analyses are needed to
determine which of the tissues making up dense tissue are related to breast cancer risk—the epithelial compartment, the stromal compartment, or both. This is a difficult task, since fewer mastectomies are being performed, and determining the percentage of these various tissues cannot, as yet, be done in vivo.

Until truly accurate 3D data are available, I would urge investigators to stop drawing conclusions based on 2D information unless the other important factors are collected at the same time to permit quantitative density and volume determinations. Without them, quantification is virtually meaningless, in my opinion. This includes investigators who are looking at overall cancer risk and those who are looking at the effect of hormones on breast density. I believe any study that has relied on measuring the proportion of dense tissue from 2D images must be viewed as not being truly accurate for the reasons I have given and illustrated. Only 3D data should be used in the future, and the claims of risk and density changes should be reevaluated.

References