



Age-Related Structural and Functional Changes in the Breast: Multimodality Correlation With Digital Mammography, Computed Tomography, Magnetic Resonance Imaging, and Positron Emission Tomography

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Preliminary results generated from digital mammography, computed tomography, magnetic resonance imaging, and ¹⁸F-fluorodeoxyglucose positron emission tomography demonstrate concordant findings of decreasing glandular tissue and decreasing metabolic activity with increasing age. These results are presented in the context of a detailed literature review summarizing age-related changes in the breast, both from the histologic/physiologic and the imaging perspectives. We also discuss potential applications of this approach and emphasize the importance of new advanced imaging technologies to offer high levels of quantitative precision for tissue characterization for research and clinical purposes. *Semin Nucl Med* 37:146-153 © 2007 Elsevier Inc. All rights reserved.

The breast is a complex organ composed of epithelial, stromal, and adipose tissue elements, the relative proportions of which vary during a woman's lifetime in response to changes in the hormonal milieu. Although age-related changes in breast composition are well-established on a qualitative level, new and emerging techniques in both anatomic and functional imaging now offer the potential for accurate quantification of such changes, with important clinical and research implications. This article presents preliminary quantitative data on age-related changes in breast tissue composition generated in our center with digital mammography, computed tomography (CT), magnetic resonance imaging (MRI), and ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET). Structural and functional imaging results were generated partially by using data that we have previously collected with an ongoing multimodality study of breast cancer. We also provide a review of the literature on

changes in breast composition over the course of time and describe the relevance of these investigations both for the research agenda and for clinical practice.

Materials and Methods

We report our preliminary results for both structural and functional changes of the breast with normal aging as determined by modern imaging techniques. Institutional review board approval for prospective and retrospective data collection and image analysis along with a HIPAA waiver were obtained from the University of Pennsylvania's Institutional Review Board before study initiation.

Structural Evaluation of Breast

Digital Mammography

Fifty-six subjects were enrolled in this study, ranging from 32 to 78 years of age. Digital mammograms were performed using a Senographe 2000D system (General Electric Medical Systems, Milwaukee, WI). A computer-assisted thresholding algorithm was used to quantitatively estimate the densities of normal breasts.¹ The values were expressed as a percentage of dense pixels over the total number of pixels comprising the entire breast. The subjects also underwent FDG-PET imag-

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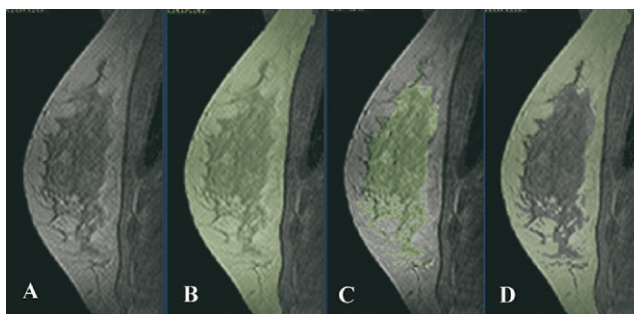


Figure 1 Breast segmentation using sagittal T1 MRI images (A). Segmentation of the whole breast (B). Segmented glandular tissue by using threshold interval (C). Segmented fatty tissue of breast (D). (Color version of figure is available online.)

ing. The FDG-PET imaging technique and image analysis are listed herein.

Linear regression analysis was performed using Microsoft Excel (Microsoft Corporation, Redmond, WA) to determine the Pearson's correlation between quantified mammographic breast densities and SUV_{avg} . In addition, the 2-tailed, unpaired Student's *t*-test was used to determine whether differences existed between subject subgroups, including pre- and postmenopausal subjects, and those with clinically dense (Breast Imaging Reporting and Data System [BI-RADS] 3,4) and nondense breasts (BI-RADS 1,2). A *P* value of less than 0.05 was considered as statistically significant.

CT

A sample of nonenhanced routine chest CT studies obtained with 5-mm axial sections in 33 women in the supine position (age range, 16-89) with no known breast pathology also were retrospectively analyzed for this study. For each examination, axial images were used to identify a 3-cm region of interest in the central left and right breasts, directly posterior to the nipple. Average attenuation value of each region of interest was measured in Hounsfield units (HU). Data for each breast were averaged and compared with age.

MRI

A sample of normal breast MRI examinations in 16 women (age range, 33-72 years) was selected for this retrospective analysis. All studies were performed on 1.5-T whole-body imaging systems in the prone position using a dedicated breast imaging coil. Images selected for analysis were segmented using 3DVIEWNIX, an open, multidimensional, multiparametric imaging software system. Before image segmentation, a variety of preprocessing algorithms were applied to the raw MR images to correct for signal intensity inhomogeneities due to RF coil field nonuniformities^{2,3} as well as to impart a standard intensity scale independent of the scanner, subject, and imaging protocol.² Unenhanced sagittal T1-weighted images were then segmented using a series of manual thresholding and editing steps to isolate glandular tissue within the breast.⁴ Percent glandular tissue for each breast was then compared with subject age (Fig. 1).

Functional Evaluation of Breast With FDG-PET

Study Sample

This report includes preliminary results from 230 subjects (average age, 50.9 ± 9.70 years; range, 32-77 years) with newly diagnosed breast cancer by radiological studies and biopsy of the lesions who were also examined with FDG-PET for detecting and staging of the primary breast cancer. The contralateral breast to the known cancer side was examined for metabolic changes that are associated with normal aging in the glandular tissues. The mean and standard deviation of ages of subjects who were premenopausal were 44.2 ± 5.71 years and those of subjects who were postmenopausal were 58.84 ± 7.11 years.

For the purposes of comparison between FDG-PET and conventional techniques, breast density was classified according to conventional mammography categories defined by BI-RADS: almost entirely fatty (group 1), scattered fibroglandular tissue (primarily fatty; group 2), heterogeneously dense (group 3), and extremely dense (group 4). Because we had very few numbers of subjects with entirely fatty and extremely dense breasts, we combined groups 1 and 2 as a nondense breast group and groups 3 and 4 as a dense breast group. Also, subjects were categorized into 2 groups according to their menopausal state as premenopausal and postmenopausal. We then determined the effects of aging and related physiological factors on breast structures. Standard statistical methods were used to determine the effects of aging and related factors on breast glandular structures. *P* values of less than 0.05 were considered to be statistically significant.

FDG-PET Imaging Protocol

PET imaging was performed 60 min after the administration of FDG as a whole-body image in either the prone or supine position, which included the entire trunk (from neck to the groin) on all subjects using a dedicated whole-body PET scanner (Allegra; Philips Medical Systems, Bothell, WA). Using a ^{137}Cs point source, transmission scans were performed to provide attenuation correction. The images were reconstructed using an iterative reconstruction algorithm. The ordered subsets-expectation maximization method was used to reconstruct the images for clinical and research analyses.

FDG-PET Image Analysis

After image reconstruction, a region of interest (ROI) was carefully drawn in the normal breast around the glandular breast tissue as determined by visual inspection on the consequent 4 to 6 PET scan slices on both sides (ROI was confined to the glandular tissue). From these ROIs, the maximum standardized uptake value (SUV_{max}) and the average SUV (SUV_{avg}) of FDG of the normal breast glandular tissue were measured. The nipple and areola were excluded while drawing ROIs (Fig. 2).

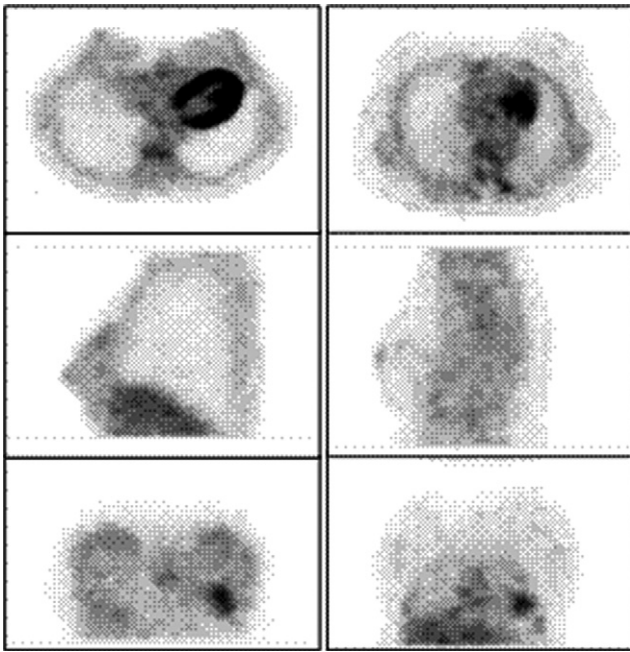


Figure 2 Relationship of SUV on FDG-PET to breast density. (A) The left column shows axial, sagittal, and coronal images of a subject with mammographically dense breasts. The measured SUV_{max} and SUV_{avg} of the glandular tissue are 1.5 and 1.0, respectively. (B) On the right demonstrates the same planes of a subject who has mammographically nondense breasts. The measured SUV_{max} and SUV_{avg} of the breast are 0.8 and 0.6, respectively. The difference between the degree of FDG uptake is also visually apparent on these images.

Results

Digital Mammography

We demonstrated a strong correlation between SUV_{avg} and quantifiable mammographic breast density, with a Pearson's correlation coefficient of 0.83. Given that mammographic breast density has been shown to decrease with age⁵ and the correlation between SUV_{avg} and mammographic breast density, it was expected that SUV_{avg} should decrease with age as well. However, given the preliminary nature of this study, the results were not statistically significant but showed a trend toward decreasing mamographic breast density and SUV_{avg} with age.

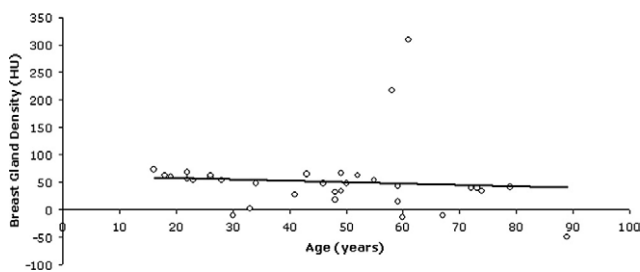


Figure 3 Breast glandular aging as measured by CT.

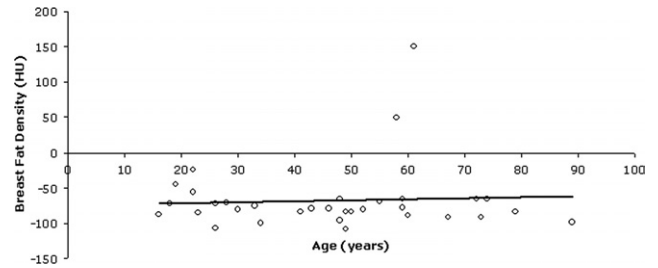


Figure 4 Effect of age on breast fatty content as measured by CT.

CT

The average central breast attenuation ranged from a maximum of 74 HU (for a 16-year-old subject) to a minimum of -50 HU (for an 89-year-old subject). The data generated on this limited sample showed a nonsignificant trend toward decreasing breast parenchymal attenuation with age (Pearson $r = -0.08$, 95% confidence interval -0.4 to 0.3; $P > 0.05$). Examples of representative graphs are given in Figs. 3 and 4.

MRI

On MRI, percent glandular tissue measured from segmented images ranged from a maximum of 28% (for a 43-year-old subject) to a minimum of 7% (for a 65-year-old subject). Data showed a nonsignificant trend toward decreasing percent glandular tissue with age (Pearson $r = -0.03$, 95% confidence interval -0.7 to 0.3; $P > 0.05$; Fig. 5).

FDG-PET

The mean and standard deviation of maximum SUVs for normal breast parenchyma were 1.16 ± 0.33 and those of average SUVs were 0.67 ± 0.20 . The SUV_{max} ranged between 0.50 and 2.30, and the SUV_{avg} ranged between 0.30 and 1.20.

Relationships of Breast Density, Menopausal Status, and Age

Mean and standard deviation of ages of subjects with dense breasts who were premenopausal were 49.0 ± 8.67 years old, and those of subjects with nondense breast were 54.0 ± 10.51 years old. Average age of subjects with nondense breasts was significantly higher than that of subjects with dense breasts ($t = 2.83$, $P < 0.01$). As a result of the known relationships between age, breast density, and menopausal status, breast density was found to correlate with the meno-

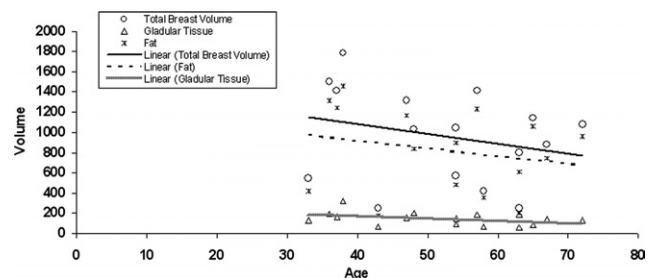


Figure 5 Breast glandular and fatty tissues compared with the total volume as determined by MRI.

pausal state ($\chi^2 = 4.66$, $P < 0.05$). No statistical differences were noted between the SUVs of the glandular tissues of the right and left breasts.

Relationships of Breast SUV With Breast Density, Age, and Menopausal Status

Breast SUV_{max} and SUV_{avg} values correlated significantly with age ($P < 0.003$) and breast density ($P < 0.018$) for both but not for menopausal state ($P < 0.245$). Simple linear regression analysis showed that breast SUV_{max} and SUV_{avg} decrease by about 0.011 units and 0.008 units per year, respectively ($P < 0.01$).

Discussion

Age-related variation in breast composition is a subject of intense interest for a number of reasons. First, multiple studies have demonstrated a correlation between breast parenchymal patterns and risk of development of breast cancer⁶; therefore, normal expected changes in breast density with age become important factors to control for in developing and refining risk prediction models. Second, breast composition has been implicated as a determinant of the accuracy of breast cancer screening, especially screening mammography,⁷ and variation in density over time has entered into the debate over when and how to conduct screening.^{8,9} Third, baseline expectations for variation in tissue composition over time will become increasingly important as imaging techniques are used to monitor parenchymal changes from new prophylactic and therapeutic interventions, including novel hormonal and pharmacologic entities.¹⁰

We have presented results from several different imaging modalities showing that with increasing age, there is a decrease in breast parenchymal density and a corresponding decrease in breast metabolic activity. Our FDG-PET results represent functional data regarding changes in breast tissue metabolic activity with aging, which correlates with anatomic imaging of breast structure. Our digital mammography, CT, and MRI results corroborate trends previously described in the literature, and also demonstrate the power of 3-D segmentation algorithms to achieve unprecedented quantitative precision in tissue characterization. The significance of these advances must be understood in the context of how research into this area has evolved over time, which will be illustrated below following a review of expected changes in breast composition with aging.

Organizational Structure of the Human Breast

The basic anatomic structure of the human breast consists of 15 to 20 lobes arranged in a circular fashion around the nipple. Each lobe drains numerous small lobules via a system of converging ducts, and each lobule contains multiple alveoli where milk is produced. The basic functional unit of the breast is the terminal duct lobular unit, which consists of the terminal duct and the lobule.

From a histological perspective, the composition of breast tissue can be divided into glandular and fatty tissue. Glandular tissue is composed of epithelial cells, which line the ductal system, and stromal elements, which provide the connective tissue framework to support the epithelium. Fatty tissue is interspersed heterogeneously between the breast lobules.¹¹ In a large study of benign breast biopsy specimens from women registered in the Nurses' Health Study, mean percentages of tissue types across all age groups were 5% epithelial, 59% stromal, and 36% adipose.¹² However, breast tissue composition varies dramatically over the lifespan in response to cellular changes induced by fluctuations in the hormonal milieu. These age-related changes in tissue composition have been studied extensively and are detailed in the next section.

Age-Related Change in the Breast: The Histologic/Physiologic Perspective

Embryologically, human breast tissue develops from the ectoderm beginning in the fourth to sixth week of fetal life. Breast tissue initially develops along the milk ridges extending from the axillae to the inguinal regions. By the ninth week of life, primitive breast tissue coalesces into 2 breast buds on the upper half of the chest. Columns of cells then invaginate inward from each breast bud, becoming separate glands with ducts leading to the nipple. Epithelial and mesenchymal differentiation subsequently occurs through a complex process of reciprocal induction.¹³

At birth, the breast will show transient enlargement to a thickness of approximately 1 cm in response to stimulation from maternal and placental hormones. For the first few weeks of life, as these hormone levels decrease, increase prolactin production from the neonatal pituitary gland will often lead to colostrum secretion from both male and female mammary glands. After stabilization of hormone levels, the breast remains functionally quiescent until puberty.¹⁴

"Thelarche," or development of mature adult mammary glands, begins in girls at puberty and continues into adolescence, reaching completion by age 20. The well-known Tanner stages describe the sequence of recognizable external changes occurring in the nipple, areola, and breast mound.¹⁵ Internally, the immature prepubertal ductal system enters into a ductal growth phase followed subsequently by a lobuloalveolar growth phase. A few years after menarche, after establishment of ovulation, the terminal duct lobular units form.

At the completion of puberty, the breast will have gone through its main growth spurt. However, as shown by Russo and Russo, full development and differentiation of the breast remain incomplete until the first full-term pregnancy.¹⁶ Histologically, the postpubertal nulliparous breast is dominated by primitive relatively undifferentiated lobular structures referred to as lobules type 1. After pregnancy, the breasts of parous women contain much higher percentages of more complex and more differentiated lobules type 2 and type 3, which are composed of greater numbers of ductular structures per lobule. If pregnancy does not occur, the breast may never attain full differentiation. The less differentiated lobule

type 1 demonstrates a higher proliferative index than lobules type 2 and 3¹⁷ and may represent the primary site of origin of ductal carcinomas as a result of greater susceptibility to carcinogenesis.¹⁸ Russo and Russo have thus suggested that the lower proportion of lobule type 1 in the breast of parous women explains the epidemiologic observation that early pregnancy is protective against breast cancer.^{19,20}

The structural changes during pregnancy and, subsequently, lactation are mediated by a complex interplay between multiple hormones, including placental hormones, estrogen, progesterone, prolactin, glucocorticoids, and oxytocin. During pregnancy, the breasts enlarge with the formation of new lobules and new alveoli organized predominantly into higher-order lobules type 2 and 3. By the second trimester of pregnancy, the alveoli differentiate into secretory units. The ability to secrete milk is reached by 15 to 20 weeks of gestation. At birth, the withdrawal of progesterone initiates lactogenesis, which is maintained and promoted by prolactin and triggered via a neuroendocrine reflex involving oxytocin. The mammary gland first produces colostrum, followed by transitional milk, followed by mature milk approximately 30 to 40 hours postpartum. After the cessation of breastfeeding, withdrawal of prolactin and oxytocin leads to postlactational involution of the gland.

Apart from the structural changes occurring around pregnancy and lactation, the breast also undergoes regular fluctuations in composition with the menstrual cycle. Cellular proliferation increases during the second part of the menstrual cycle,²¹ leading to increases in glandular volume and water content.²² This change is conspicuous enough to be seen both mammographically²³ and by gadolinium-enhanced MRI.²⁴ Although cellular proliferation is followed predictably by cell death at the end of the menstrual cycle,²⁵ mammary development during a menstrual cycle never fully returns to the starting point of the preceding cycle. Accordingly, each ovulatory cycle fosters slightly more mammary development, with new budding of structures continuing until about age 35.¹⁶

After the early childbearing years, however, the breast undergoes slow, steady involution, accompanied by observable changes in histology. In nulliparous women, lobule type 1 remains the predominant structure throughout the lifespan, while lobule type 2, present in moderate numbers during the early years, begins to decrease as early as age 23. In parous women, lobule type 3 remains the predominant structure until the age of 40, after which time the breast undergoes gradual involution to lobules type 2 and 1.¹⁶

The regression in breast parenchyma is accelerated at menopause, which occurs on average around age 52. Loss of endogenous estrogen and progesterone stimulates involution of glandular epithelium via apoptosis, with islands of ductal tissue left behind. There is a concurrent loss of lymphatics, and the stroma is replaced by fat. In the Nurses' Health Study investigation referenced above, percentage of glandular tissue (ie, epithelial and stromal elements) in benign breast biopsy specimens decreased from 75% in women younger than 30 to 67% in women ages 41 to 50 years to 43% in women older than age 60 years, thus confirming regression of

breast tissue in premenopausal women and acceleration of tissue regression at menopause.¹²

Postmenopausal exposure to exogenous hormones has a predictable effect on tissue composition, which is dependent on interaction with estrogen receptors. Although hormone replacement with exogenous estrogen increases the mammographic density of the breast,^{26,27} selective estrogen receptor modulators (eg, tamoxifen and raloxifene) with antagonistic effects on estrogen receptors in the breast have been shown to reduce mammographic density.^{10,28}

In summary, the breast evolves over the lifespan in a dynamic and complex fashion. The general trend is one of rapid anatomic development at puberty and completion of differentiation at the first full-term pregnancy, followed by slow, gradual glandular involution and structural dedifferentiation beginning in the childbearing years and accelerating at menopause. The following section reviews how these age-related changes in the breast have been documented by different imaging modalities.

Age-Related Change in the Breast: The Structural Imaging Perspective

Imaging of age-related variation in breast composition has evolved over time, from qualitative categorization of breast density using conventional mammography, to quantitative planimetric assessments using digital mammography, to more sophisticated quantitative evaluation using 3-D segmentation with cross-sectional techniques such as MRI. Each successive development in imaging technology has brought a higher degree of precision in characterizing the subtle changes occurring in breast tissue over the lifespan.

The earliest attempts to examine variations in breast composition used qualitative assessment of breast density from film-screen mammograms. In 1976, Wolfe organized the mammographic appearance of breast parenchyma into 4 qualitative categories—N1, P1, P2, and DY—in an attempt to correlate gross radiographic appearance with risk of subsequent breast cancer.²⁹ In Wolfe's initial studies, the number of women in the densest parenchymal categories decreased significantly with age,³⁰ especially in premenopausal women.⁵ Successive studies confirmed these results,³¹⁻³³ with some investigators also showing different rates of parenchymal regression for different racial groups.³⁴

Wolfe's classification system was inherently subjective, however, and his qualitative classification system was applied inconsistently, with variable interobserver and intraobserver agreement.³⁵ To address this problem, the next generation of studies on breast parenchymal patterns sought better agreement for visual assessment by asking readers to estimate visually the percentage of breast occupied by glandular tissue. Purely qualitative categories were thus replaced with semi-quantitative ones, such as the six categories of density used in the Canadian National Breast Screening Study.³⁶ Again, these studies demonstrated a progressive decrease in parenchymal density with age in both premenopausal and postmenopausal age cohorts.⁸ These studies also strengthened the correlation between radiology and histology, establishing stromal prolif-

eration as the feature most consistently associated with changes in mammographic density.³⁷ Visual estimation of percent glandular tissue was later incorporated into the clinical mammography reporting standards developed by the American College of Radiology in its BI-RADS initiative.³⁸

The next step in the evolution of imaging age-related tissue changes of the breast replaced visual estimates of glandular tissue with actual calculations of percent density. These techniques adopted planimetric methods, in which regions of interest were drawn about the glandular portions of the breast either manually³⁹ or by interactive, computer-assisted thresholding tools.¹ These methods yielded higher levels of agreement among readers and produced a number of studies demonstrating a decrease in percent density with age and a correlation between mammographic density and risk of subsequent breast cancer.³⁵

The inherent limitation of planimetric methods, however, is that calculations of percent glandular tissue are computed from 2-D projection images. As pointed out by Harvey and coworkers³⁵ even a high-resolution digital mammographic image must be processed as set of binary pixels (either fat or parenchyma) without accounting for the depth of fat or parenchyma in the plane orthogonal to the pixel. Measurement of breast composition, therefore, has now evolved to three-dimensional measurements using cross-sectional imaging techniques. The current state-of-the-art involves acquisition of 3-D data sets and segmentation of tissue via advanced computer-based algorithms, an approach that allows for a high degree of quantitative precision in calculating tissue composition. Lee and coworkers, for example, segmented 3-D MR images and found a direct relationship between increasing age and the percentage of breast comprised by fatty tissue, with an average increase in adipose content of 6.5% per decade; the correlation was weak, however, with a standard error of 16%,⁴⁰ probably reflecting the variability in tissue composition within age cohorts. Muller-Schimpfle and coworkers²⁴ found that MRI parenchymal contrast enhancement is significantly higher in subjects ages 35 to 50 years than in subjects younger than 35 or older than 50 years. Other investigators have proposed using ultrasonography⁴¹ or dual x-ray absorptiometry to measure breast density, and our institution is presently conducting preliminary research using contrast-enhanced digital breast tomosynthesis.⁴²

Age-Related Change in the Breast: The FDG-PET Perspective

Vranjesevic and coworkers retrospectively analyzed the effects of breast density on FDG uptake in 45 women with normal breast tissue.⁴³ They concluded that breast density and hormonal state affect the uptake of FDG, and that SUVs are significantly greater in dense breasts compared with fatty breasts. However, they were unable to show a correlation between age and SUV in normal breast tissue.

Our data demonstrated that there is a significant decrease of FDG uptake as age increases. This study is the first, to our knowledge, that shows a correlation between age and ¹⁸F-FDG uptake in the breast tissue. The radiographic data in

our study population further confirmed those of previous studies in the mammography literature, which showed that older women tend to have fatty breasts. Based on our data, there was an inverse correlation between age and mammographic breast density, which has previously been well documented in the literature.

According to our results, menopausal state has no effect on FDG uptake in the breast. In the study of Vranjesevic, the authors reported that breasts of premenopausal women had a higher SUV than breasts of postmenopausal women not receiving hormonal therapy. In contrast, postmenopausal women receiving hormonal therapy had SUVs similar to those of the premenopausal women. Thus, they concluded that hormonal therapy in postmenopausal women appears to normalize the glucose metabolic activity of normal breast tissue.⁴³ In our study we had no subjects who were receiving hormonal therapy. Therefore, we could not determine the effect of hormonal therapy in the postmenopausal group of women. However, hormone replacement therapy and/or hormonal stimuli have been reported to increase breast density in literature.^{44,45} Therefore, we believe that further studies are necessary with postmenopausal subjects who are on hormone therapy to determine the combined effect of age and this therapeutic intervention on breast SUV.

In addition, data from Vranjesevic revealed that FDG uptake was slightly, but significantly, greater in the right breast than in the left breast. On average, they found that the metabolic activity in the left breast was approximately 10% lower than that in the right breast.⁴³ Our results showed that there is no significant difference between FDG uptake between the 2 breasts.

Toward a Unified Understanding of Age-Related Change in the Breast

Our results from digital mammography, CT, MRI, and FDG-PET confirm the expected findings of progressively involuting parenchymal tissue with increasing age, leading to decreasing breast density when measured by plain film radiography or CT, decreasing percent glandular tissue when measured by MRI, and decreasing metabolic activity when measured with FDG-PET. These results are concordant with predictions from current knowledge regarding the evolution of breast histology and physiology, and contribute toward a holistic radiologic-pathologic understanding of changes in breast tissue over the lifespan. Our results also illustrate the emerging capability of advanced imaging technologies to quantify these changes with high levels of precision at the structural and functional levels. Such quantification will be necessary for many of the potential future applications discussed in the final section.

The biggest limitation to studying age-related changes in the breast is the high degree of variability in breast composition within an age cohort. Because of this great variability, study designs such as our own often produce clear trends yet lack the large sample size needed to meet criteria for statistical significance. Other investigators have encountered similar difficulty,^{24,40} noting high degrees of variability within age

cohorts, and Powell and coworkers found in their study involving computer segmentation of digital mammograms that variability within an age cohort was enough to overwhelm differences in breast composition with age.⁴⁶ Some investigators have used longitudinal study designs, following a cohort of women over time,^{32,33,47} but these studies are time-consuming and costly to perform and are thus vanishingly rare.⁴⁸ We hope that the preliminary results presented in this article will galvanize interest in performance of larger prospective studies in the future regarding age-related changes in the breast and other determinants of breast composition including pregnancy, body mass index, nutrition, and environmental effects.

Applications of Advanced Imaging Techniques to the Breast

This article has reviewed the spectrum of normal expected changes in breast structure and function with aging and has described and illustrated a number of techniques for measuring these changes over time. We have presented primary data demonstrating a decrease in parenchymal volume and metabolic activity as a function of age, and have emphasized state-of-the-art developments in quantitative analytic modalities including FDG-PET and segmented 3D MRI. As they are refined and offer more and more quantitative precision, we expect incorporation of these techniques to occur into a broad array of research and clinical applications.

First, these quantitative modalities will facilitate further exploration of the factors affecting variability in breast composition. Avenues of potential investigation include breast composition variability over the menstrual cycle, during and after pregnancy and with lactation, and around menarche and around menopause. These techniques may also be incorporated into twin studies to separate the relative influences of genetic and environmental factors on breast structure and function. Quantitative imaging may be used to test alternative hypotheses surrounding breast differentiation, for example, by evaluating the response of breast tissue to different hormonal environments in animal models.

Second, these imaging techniques may also be incorporated in the future into risk assessment algorithms for patients. Current risk assessment tools rely on nonspecific variables such as age at menarche, age at first live birth, and family history⁴⁹ and do not incorporate any information regarding actual breast architecture. Since the vast majority of breast cancers arise in epithelial tissue, and since breast density is known to be an independent predictor of cancer development,^{6,50} assessment of the relative proportion and function of glandular tissue may play a direct role in predicting breast cancer risk. Further research will elucidate whether there is a relationship between metabolic activity and the presence of cellular atypia, which would place a patient at a higher risk for malignancy. Measurement of breast structure and function may also play a role in developing more "personalized" breast cancer screening strategies, eg, women with high percentages of glandular tissue or abnormally high baseline metabolic activity may receive earlier

or more frequent mammographic screening, or may be triaged to screening with cross-sectional modalities like ultrasonography or MRI.

Finally, advanced imaging modalities may be used in the design, evaluation, and monitoring of preventive and therapeutic agents for breast cancer. Quantitative imaging techniques may be used early in the drug discovery process to evaluate the response of breast tissue to pharmacologic manipulation of hormonal receptors and the hormonal environment.⁵¹ Information on breast composition may also be used in the setting of breast cancer prevention and treatment trials, either as entry criteria or as surrogate outcome markers.³⁵ In the future, continuing research of normal variations with age will provide important benchmarks against which metabolic and morphologic results in the setting of disease states will be compared.

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