Relationship Between ^{18}F-FDG Uptake and Breast Density in Women with Normal Breast Tissue

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Breast density affects the mammographic detectability of breast cancer. The study aimed to evaluate the impact of breast density on the ^{18}F-FDG uptake of normal breast tissue. **Methods:** The study population consisted of 45 women (median age, 54 y; age range, 42–77 y). All underwent whole-body ^{18}F-FDG PET for various indications other than breast cancer, and all underwent mammography within a mean of 6.6 ± 4.9 mo of PET. On the basis of mammographic findings, breasts were categorized as extremely dense, heterogeneously dense, primarily fatty, or entirely fatty. Regions of interest were drawn on every PET image in which breast tissue was visualized. Average and peak standardized uptake values (SUVs) were calculated for the left and right breasts. **Results:** Mammography showed that 20 of the 45 women had heterogeneously dense breasts, 1 had extremely dense breasts, 20 had primarily fatty breasts, and 4 had entirely fatty breasts. In dense breasts, the average SUV was 0.39 ± 0.05 (right breast) and 0.36 ± 0.07 (left breast) and the peak SUV was 0.93 ± 0.16 and 0.89 ± 0.18, respectively. The average and peak SUVs were significantly lower for primarily fatty breasts than for dense breasts ($P < 0.01$). Peak and average SUVs of entirely fatty breasts also differed significantly from peak and average SUVs of dense and primarily fatty breasts ($P < 0.01$). The impact of hormonal status on SUV was significant but less than the impact of breast density. No significant relationship between average SUV or peak SUV and age or serum glucose level was observed. **Conclusion:** Breast density and hormonal status affect the uptake of ^{18}F-FDG. Dense breasts exhibit, on average, significantly higher ^{18}F-FDG uptake than do nondense breasts. However, the highest peak SUV observed in dense breasts was 1.39, which is well below the SUV of 2.5 commonly used as a cutoff between benign and malignant tissue. Therefore, breast density is unlikely to affect the ability of ^{18}F-FDG PET to discriminate between benign and malignant breast lesions.

Key Words: ^{18}F-FDG PET; dense breast; standardized uptake value

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Mammography reduces breast cancer mortality (*1*) but, especially in women with dense breasts, has limited diagnostic accuracy, which results in a considerable number of missed cancers. Breast density is a measure of stromal and epithelial breast tissue (*2*) and is classified into 1 of 4 groups as defined by the Breast Imaging Reporting and Data System (BI-RADS): almost entirely fatty (group 1), scattered fibroglandular tissue (primarily fatty) (group 2), heterogeneously dense (group 3), and extremely dense (group 4).

Mammography detects breast cancer with sensitivities ranging from only 30% to 68% in women with dense or very dense breasts (*3–5*). In women aged 50–64 y who had dense breasts and had undergone estrogen replacement, the sensitivity was 55%. Mandelson et al. (*4*) reported sensitivities for breast cancer detection of 80%, 59%, and 30% in women with, respectively, predominantly fatty breast tissue, heterogeneously dense breasts, and extremely dense breasts. The authors concluded that "breast density is one of the strongest, if not the strongest, predictor of the failure of mammographic screening to detect cancer." Foxcroft et al. (*5*) reported similar limitations for mammographic screening and recommended that women with dense breasts should undergo different screening tests. The risk of breast cancer in mammographically dense breasts cannot be solely explained by the masking of cancer by dense tissue. John Wolfe (*6*) was the first to establish a relationship between breast density and breast cancer risk. This finding has been reproduced in many studies (*7–10*). Warner et al. (*11*) conducted a metaanalysis of the published literature to determine the magnitude of the risk of breast cancer associated with breast density. The authors concluded that breast density is an independent risk factor for breast cancer. In fact, the relative risk for breast cancer in women with extremely dense and heterogeneously dense breasts after adjusting for menopausal status, age, hormone replacement therapy (HRT), and other parameters was 5.3 and 3.4, respectively, compared with a relative risk of 1 in women with predominantly fatty breasts (*8*).

TABLE 1
Average and Peak SUV for Different Breast-Density and Menopausal-Status Groups

Group	*n*	Average SUV		Peak SUV	
		Right breast	Left breast	Right breast	Left breast
Dense	21	0.39 ± 0.05	0.36 ± 0.07	0.93 ± 0.16	0.89 ± 0.18
Primarily fatty	20	0.32 ± 0.10	0.31 ± 0.08	0.80 ± 0.22	0.75 ± 0.20
Entirely fatty	4	0.22 ± 0.07	0.22 ± 0.09	0.51 ± 0.06	0.53 ± 0.13
Premenopausal	12	0.34 ± 0.08	0.35 ± 0.09	0.98 ± 0.27	0.91 ± 0.24
Postmenopausal (no HRT)	12	0.28 ± 0.06	0.31 ± 0.08	0.76 ± 0.17	0.71 ± 0.14
Postmenopausal (HRT)	12	0.37 ± 0.10	0.36 ± 0.05	0.85 ± 0.20	0.84 ± 0.22

Because of the limited sensitivity of mammography in women with dense breasts, other imaging modalities such as ultrasound and MRI have been proposed as additional diagnostic tools for improving breast cancer detection. These techniques might increase the sensitivity, but there is no definitive evidence that they result in improved breast cancer detection.

^{18}F-FDG PET characterization of palpable breast masses or mammographic abnormalities is highly accurate (*12–18*). However, breast density might affect not only mammographic performance for breast cancer detection but also ^{18}F-FDG uptake in normal breast tissue. This has not been studied systematically. Because increased ^{18}F-FDG uptake might alter the detectability of breast cancer with PET, the aim of our study was to evaluate whether the ^{18}F-FDG uptake pattern of normal breast tissue is affected by breast density.

MATERIALS AND METHODS

Forty-five consecutive female patients (median age, 54 y; age range, 42–77 y) who were undergoing whole-body PET were included in the study if they had no history of breast cancer or any other breast disease and had a recent mammogram. Patients underwent whole-body ^{18}F-FDG PET for various indications, that is, malignancies other than breast cancer ($n = 18$), whole-body surveys for suspected cancer ($n = 20$), or screening to rule out malignancies ($n = 7$). None of the cancer patients had undergone chemotherapy or radiation therapy within a median interval of 10 wk (range, 7–30 wk) of PET. None of the PET scans had abnormal findings in the region of the breasts. Subjects underwent mammography within a mean interval of 6.6 ± 4.9 mo of PET. The menopausal status and HRT data were known for 36 of the 45 women.

PET was performed using an ECAT EXACT HR or HR+ system (CTI/Siemens). All women fasted for at least 6 h before the intravenous administration of 370–555 MBq of ^{18}F-FDG. The imaging protocol was identical for each patient. The image acquisition started at 45 min after tracer injection. Images were acquired in 2-dimensional mode over 6–8 bed positions from the base of the skull to the mid thigh. Emission data were acquired for 6 min/bed position and transmission data for 3 min/bed position. The breasts were in the field of view 63 min after injection.

The PET systems were quantitatively calibrated on a quarterly basis using the vendor-recommended procedure, which involves the scanning of a uniform 20-cm-diameter and 20-cm-tall cylinder filled with a known amount of ^{68}Ge. The quantitative accuracy was monitored on a daily basis as part of the daily quality control procedure (*19*).

Standardized uptake values (SUVs) for ^{18}F-FDG were calculated for regions of interest encompassing both breasts using the standard formula (*20*). Specifically, regions of interest were drawn around the breasts on every axial image plane in which breast tissue was visualized. The average SUV was calculated from all image planes for each patient about 1 h after tracer injection. The peak SUV was derived from the single image plane that had the highest average SUV. The nipple and areola area were excluded from region-of-interest placement. Average and peak SUVs were calculated for the left and right breasts. Corrections for lean body mass and body surface area were applied as follows: lean body mass (kg) = $1.07 \times$ (weight [kg]) $-$ 148 (weight [kg]/height [cm])^2 (*21*), and body surface area (m^2) = (weight [kg])$^{0.425} \times$ (height [cm])$^{0.725} \times 0.007184$ (*22*). The range of body weights was 41.8–109.0 kg. Six of the patients (13%) weighed more than 80 kg.

Bilateral screening mammography was performed with mediolateral–oblique and craniocaudal views for all women. If necessary, additional views were obtained for clarification. Mammograms were analyzed visually, and breast tissue was classified as extremely dense, heterogeneously dense, scattered fibroglandular (i.e., primarily fatty), or entirely fatty. The written radiology reports were used to retrieve the breast density and BI-RADS classification of the mammograms.

Differences between patient groups and subsets were analyzed using the Student *t* test. A *P* value of less than 0.05 was considered statistically significant. Stepwise multiple-regression analysis was performed using SUV, glucose levels, menopausal status, breast density, and age as variables. Linear regression analysis was used to investigate the effect of SUV correction for lean body mass or body surface area. Interobserver variability was also evaluated using linear regression analysis.

RESULTS

Twenty of the 45 women had heterogeneously dense breasts, 1 had extremely dense breasts, 20 had primarily fatty breasts, and 4 had entirely fatty breasts. Because of the small number of patients in some of the subsets, the data for extremely dense breasts were merged with the data for heterogeneously dense breasts to establish 1 group termed *dense breasts.* Both average and peak SUV were higher for dense breasts than for primarily fatty ($P < 0.01$) or entirely fatty breasts ($P < 0.01$) (Table 1). SUVs were lower for the

left than the right breast (Table 1; Fig. 1). The difference between left and right breast was significant for women with entirely fatty breasts, primarily fatty breasts, or dense breasts ($P < 0.05$).

Menopausal status was known for 36 women, and their average and peak SUVs were comparable to those of the 9 women whose menopausal status was not known. Inspection of the different subsets (premenopausal, postmenopausal with HRT, and postmenopausal without HRT) showed that hormonal status affected ^{18}F-FDG uptake (Table 1). Postmenopausal women receiving HRT had peak and average SUVs similar to those of premenopausal women, whereas the SUVs of postmenopausal women not receiving hormone replacement were significantly lower ($P < 0.05$).

Because mammographic breast density is related to age, the relationship between peak and average SUV and age was investigated (Fig. 2). This analysis revealed no significant correlation between age and average or peak SUV.

It is well known that serum glucose levels affect ^{18}F-FDG uptake in a variety of tumors (*23*). In all women, the glucose level was measured at the time of injection and varied between 56 and 130 mg/dL. No significant relationship was found between serum glucose level and SUV ($r = 0.18$; $P =$ not statistically significant). Thus, serum glucose levels did not affect ^{18}F-FDG uptake in normal breast tissue.

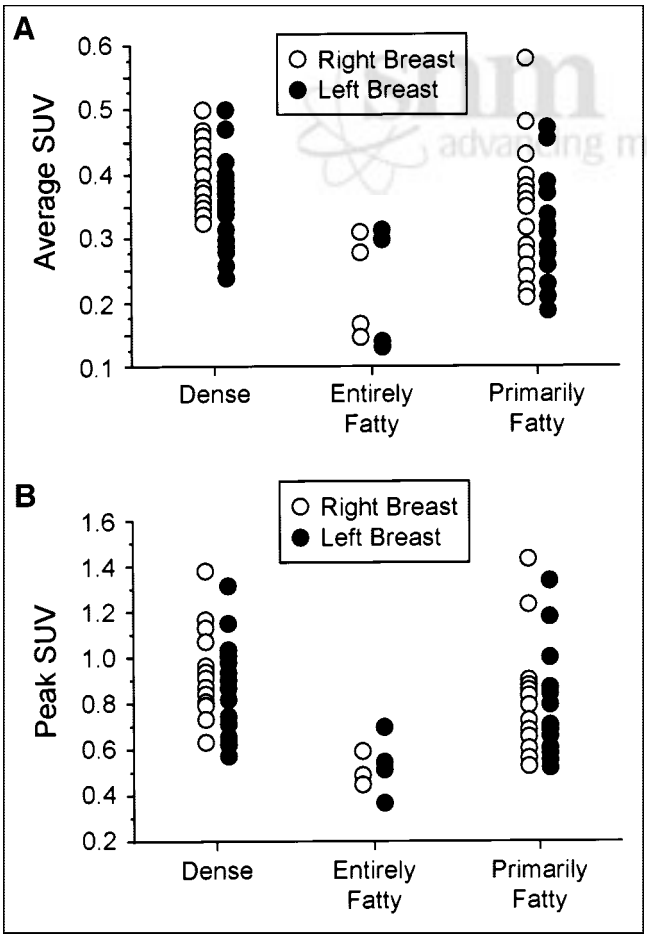

FIGURE 1. Average SUV (A) and peak SUV (B) plotted for different breast-density groups. Data are presented separately for left and right breasts. Entirely fatty breasts had lowest SUVs.

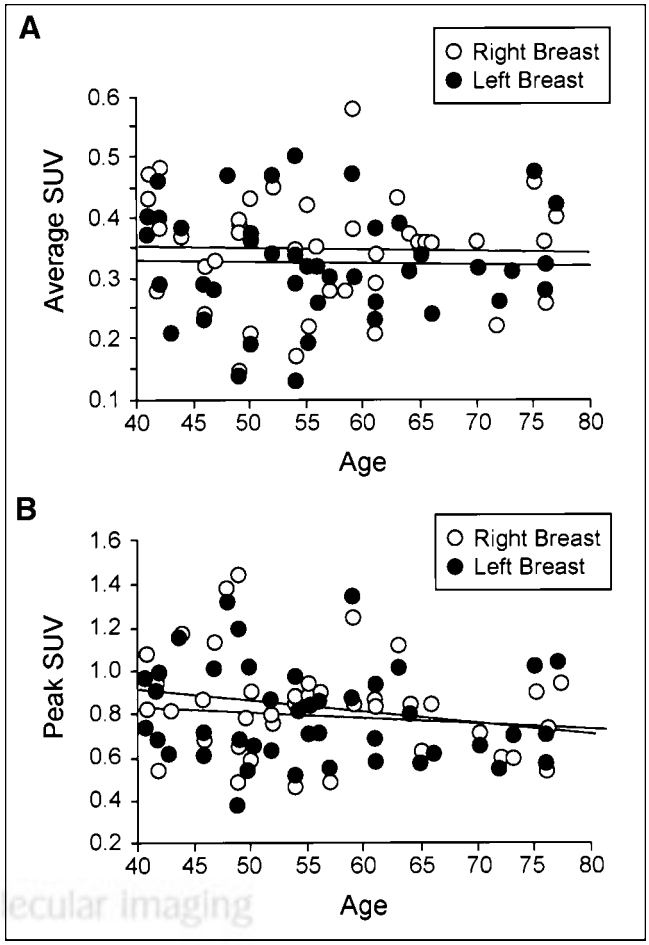

FIGURE 2. Average SUV (A) and peak SUV (B) as function of age. Linear regression lines are given separately for left and right breasts. No regression slopes differed significantly from horizontal (slope = 0). Age does not appear to be a factor in normal breast glycolytic activity.

The ^{18}F-FDG uptake values in Table 1 and Figures 1 and 2 are based on total body weight. Correction of the SUVs for lean body mass and body surface area was also applied. Linear regression analyses between SUVs (both corrected and uncorrected) and total body weight furnished slopes that did not differ significantly from zero, after correction for multiple comparisons was applied. Figure 3 shows a high correlation between corrected and uncorrected SUVs ($r = 0.92$).

Stepwise multiple regression analysis revealed that breast density and hormonal status were predictive variables. Breast density correlated significantly with breast ^{18}F-FDG uptake ($r = 0.65$ and $P < 0.001$ for average SUV; $r = 0.46$ and $P = 0.015$ for peak SUV). To assess the effect of hormonal status, the premenopausal and postmenopausal women receiving HRT were pooled and compared with the postmenopausal women not receiving HRT. Hormonal sta-

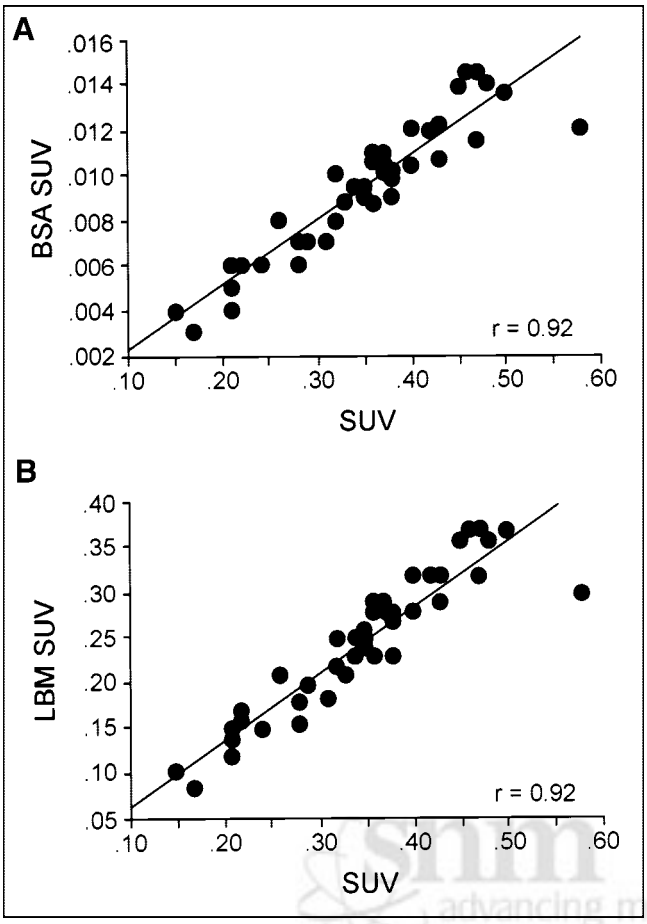

FIGURE 3. Scattergrams of uncorrected SUV of normal breast tissue versus SUV corrected for lean body mass (LBM) (A) or body surface area (BSA) (B). Note high correlation coefficients.

tus correlated significantly with ^{18}F-FDG uptake ($r = 0.46$ and $P = 0.02$ for average SUV; $r = 0.36$ and $P = 0.01$ for peak SUV). None of the other variables showed statistically significant correlations. The use of average ^{18}F-FDG uptake as a dependent variable showed that density was the strongest predictor of SUV (41% explained variance), followed by hormonal status (19% explained variance). In Figure 4, transverse slices of typical breasts in the 3 density categories are given.

DISCUSSION

To our knowledge, this was the first study to examine the impact of breast density on ^{18}F-FDG uptake in normal breast tissue. The study revealed that ^{18}F-FDG uptake in normal breast tissue, as expressed by the SUV, is affected by breast density. Hormonal status also had a significant impact on SUV, but to a lesser degree. The metabolic activity of normal dense breast tissue was low; the highest peak SUV encountered was 1.39, and the average SUVs were around 0.4 (Table 1). Thus, the highest peak SUV was well below the threshold value of 2.0–2.5 that is frequently used as a cutoff point for discriminating benign from malignant lesions. Thus, breast density affects ^{18}F-FDG uptake but is unlikely to affect breast cancer detectability. Avril et al. (*24*) have systematically analyzed ^{18}F-FDG uptake in benign and malignant primary breast lesions. In malignant tumors, a mean SUV of 3.3 ± 1.8 was reported, whereas in benign breast tumors, the mean SUV was 1.4 ± 0.5. This difference in tumor SUVs was statistically significant ($P < 0$ 0.01). However, no systematic analysis of SUVs of normal breast tissue was conducted.

In the current study, average ^{18}F-FDG uptake was slightly, but significantly, higher in the right breast than in the left breast (Fig. 1). The stepwise regression analysis revealed significant left–right asymmetries for the different breast-density groups. A possible explanation for this observation could be the proximity of the heart (cross talk or spillover). The myocardium had high uptake in all women with dense breasts and in most of the other women (75%). To further evaluate this asymmetry, a phantom experiment was performed and a possible effect of acquisition and reconstruction parameters on SUVs was investigated. A thorax phantom containing Styrofoam (The Dow Chemical Co.) to simulate the lungs, a heart phantom, and breast inserts was filled with activity typical for the clinical situation. The heart-to-breast uptake ratio was approximately 4. The same iterative reconstruction algorithm was used as for patient studies. No left–right asymmetries were found in the breast inserts, rendering a technical effect or reconstruction-induced artifact unlikely. Therefore, it seems that the observed small but significant left–right asymmetry was real.

On average, the metabolic activity in the left breast was about 10% lower than that in the right breast. Stabin and Breitz (*25*) reported that the left female breast is larger than the right. The original article they referred to (*26*) found a difference of 10%–15%. A search of the more recent literature did not provide additional studies to corroborate this observation. An average increase in size, which translates into more fat present, could explain the 10% difference in observed metabolic activity.

Because the prevalence of mammographically dense breasts declines with age (*27–29*) and dense breast tissue is more common before than after menopause (*29–32*), it has been suggested that menopausal or hormonal status, rather than age, is the most important determinant of breast density (*30*). Consistently, the current study found no significant

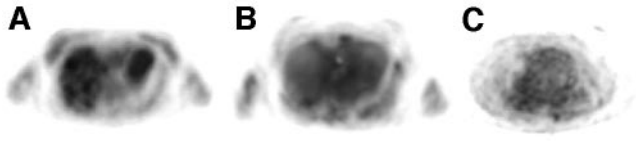

FIGURE 4. Typical breasts in the 3 density categories. Transverse slices of dense (A), primarily fatty (B), and entirely fatty (C) breasts are shown. Region of areola has increased uptake relative to remainder of breast. Note decreasing ^{18}F-FDG uptake from A to B, with clear photopenia in area of entirely fatty breasts (C).

correlation between age and ^{18}F-FDG uptake, whereas a significant relationship between ^{18}F-FDG uptake and hormonal status was observed.

Of the 36 women with known menopausal status, 12 were premenopausal, 12 were postmenopausal and not receiving HRT, and 12 were postmenopausal and receiving HRT. Breasts of premenopausal women had a higher SUV than breasts of postmenopausal women not receiving HRT. In contrast, postmenopausal women receiving HRT had SUVs similar to those of the premenopausal women. Thus, HRT in postmenopausal women appears to normalize the glucose metabolic activity of normal breast tissue.

As suggested by Zasadny and Wahl (*33*), correction for body surface area or lean body mass is necessary to calculate the SUVs of tumors and to standardize ^{18}F-FDG uptake for patient habitus, remove the effect of tissues with low ^{18}F-FDG activity such as fat, and allow direct comparison between patients. In our study, we did not find significant differences in the SUVs of normal breast tissue using total body weight, lean body mass, or body surface area. The corrected and uncorrected SUVs showed excellent correlation (Figs. 3A and 3B). In clinical practice, therefore, there is no need to correct the SUV for normal breast tissue. This finding is consistent with observations by Zasadny and Wahl, who reported that normal tissues with substantial ^{18}F activity (mean SUV $>$ 1.9) correlate positively with total body weight, whereas SUVs in tissues with less ^{18}F activity (mean SUV around 1) do not correlate with body weight.

This study had some limitations. The regions of interest were drawn manually, an approach that is well known to be observer dependent. Two observers analyzed the data independently and without knowing the results of mammography. The measurements were stable, and the interobserver variability was low ($r = 0.94$; $P < 0.0001$), emphasizing the excellent reproducibility.

CONCLUSION

The glucose metabolic rate of normal breast tissue is low. Breast density and hormonal status affect uptake of ^{18}F-FDG. However, the ability to discriminate benign from malignant disease is unlikely to be affected by breast density, since the calculated average SUVs were low and peak SUV never exceeded 1.5.

REFERENCES

1. Fletcher SW, Black W, Harris R, Rimer BK, Shapiro S. Report of the International Workshop on Screening for Breast Cancer. *J Natl Cancer Inst.* 1993;85: 1644–1656.
2. Boyd NF, Lockwood GA, Martin LJ, Byng JW, Yaffe MJ, Tritchler DL. Mammographic density as a marker of susceptibility to breast cancer: a hypothesis. *IARC Sci Publ.* 2001;154:163–169.
3. Rosenberg RD, Hunt WC, Williamson MR, et al. Effects of age, breast density, ethnicity, and estrogen replacement therapy on screening mammographic sensitivity and cancer stage at diagnosis: review of 183,134 screening mammograms in Albuquerque, New Mexico. *Radiology.* 1998;209:511–518.
4. Mandelson MT, Oestreicher N, Porter PL, et al. Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers. *J Natl Cancer Inst.* 2000;92:1081–1087.
5. Foxcroft LM, Evans EB, Joshua HK, Hirst C. Breast cancers invisible on mammography. *Aust N Z J Surg.* 2000;70:162–167.
6. Wolfe JN. Breast patterns as an index of risk for developing breast cancer. *AJR.* 1976;126:1130–1137.
7. Byrne C, Schairer C, Wolfe J, et al. Mammographic features and breast cancer risk: effects with time, age, and menopause status. *J Natl Cancer Inst.* 1995;87: 1622–1629.
8. Boyd NF, Lockwood GA, Byng JW, Tritchler DL, Yaffe MJ. Mammographic densities and breast cancer risk. *Cancer Epidemiol Biomarkers Prev.* 1998;7: 1133–1144.
9. Saftlas AF, Hoover RN, Brinton LA, et al. Mammographic densities and risk of breast cancer. *Cancer.* 1991;67:2833–2838.
10. Saftlas AF, Szklo M. Mammographic parenchymal patterns and breast cancer risk. *Epidemiol Rev.* 1987;9:146–174.
11. Warner E, Lockwood G, Tritchler D, Boyd NF. The risk of breast cancer associated with mammographic parenchymal patterns: a meta-analysis of the published literature to examine the effect of method of classification. *Cancer Detect Prev.* 1992;16:67–72.
12. Flanagan FL, Dehdashti F, Siegel BA. PET in breast cancer. *Semin Nucl Med.* 1998;28:290–302.
13. Delbeke D. Oncological applications of FDG PET imaging. *J Nucl Med.* 1999; 40:1706–1715.
14. Adler LP, Crowe JP, al-Kaisi NK, Sunshine JL. Evaluation of breast masses and axillary lymph nodes with [F-18] 2-deoxy-2-fluoro-D-glucose PET. *Radiology.* 1993;187:743–750.
15. Hoh CK, Schiepers C. 18-FDG imaging in breast cancer. *Semin Nucl Med.* 1999;29:49–56.
16. Scheidhauer K, Scharl A, Pietrzyk U, et al. Qualitative [^{18}F]FDG positron emission tomography in primary breast cancer: clinical relevance and practicability. *Eur J Nucl Med.* 1996;23:618–623.
17. Tse NY, Hoh CK, Hawkins RA, et al. The application of positron emission tomographic imaging with fluorodeoxyglucose to the evaluation of breast disease. *Ann Surg.* 1992;216:27–34.
18. Nieweg OE, Kim EE, Wong WH, et al. Positron emission tomography with fluorine-18-deoxyglucose in the detection and staging of breast cancer. *Cancer.* 1993;71:3920–3925.
19. Meikle SR, Bailey DL, Hooper PK, Fulham MJ. Accelerated EM reconstruction in total-body PET: potential for improving tumour detectability. *Phys Med Biol.* 1994;39:1689–1704.
20. Schomburg A, Bender H, Reichel C, et al. Standardized uptake values of fluorine-18 fluorodeoxyglucose: the value of different normalization procedures. *Eur J Nucl Med.* 1996;23:571–574.
21. Morgan DJ, Bray KM. Lean body mass as a predictor of drug dosage: implications for drug therapy. *Clin Pharmacokinet.* 1994;26:292–307.
22. Kim CK, Gupta NC, Chandramouli B, Alavi A. Standardized uptake values of FDG: body surface area correction is preferable to body weight correction. *J Nucl Med.* 1994;35:164–167.
23. Wahl RL, Henry CA, Ethier SP. Serum glucose: effects on tumor and normal tissue accumulation of 2-[F-18]-fluoro-2-deoxy-D-glucose in rodents with mammary carcinoma. *Radiology.* 1992;183:643–647.
24. Avril N, Dose J, Janicke F, et al. Metabolic characterization of breast tumors with positron emission tomography using F-18 fluorodeoxyglucose. *J Clin Oncol.* 1996;14:1848–1857.
25. Stabin MG, Breitz HB. Breast milk excretion of radiopharmaceuticals: mechanisms, findings, and radiation dosimetry. *J Nucl Med.* 2000;41:863–873.
26. Smith DJ Jr, Palin WE Jr, Katch VL, Bennett JE. Breast volume and anthropomorphic measurements: normal values. *Plast Reconstr Surg.* 1986;78:331–335.
27. Oza AM, Boyd NF. Mammographic parenchymal patterns: a marker of breast cancer risk. *Epidemiol Rev.* 1993;15:196–208.
28. Krook PM. Mammographic parenchymal patterns as risk indicators for incident cancer in a screening program: an extended analysis. *AJR.* 1978;131:1031–1035.
29. Wolfe JN. Breast parenchymal patterns and their changes with age. *Radiology.* 1976;121:545–552.
30. Grove JS, Goodman MJ, Gilbert FI Jr, Mi MP. Factors associated with mammographic pattern. *Br J Radiol.* 1985;58:21–25.
31. Hart BL, Steinbock RT, Mettler FA Jr, Pathak DR, Bartow SA. Age and race related changes in mammographic parenchymal patterns. *Cancer.* 1989;63:2537–2539.
32. Brisson J, Merletti F, Sadowsky NL, Twaddle JA, Morrison AS, Cole P. Mammographic features of the breast and breast cancer risk. *Am J Epidemiol.* 1982; 115:428–437.
33. Zasadny KR, Wahl RL. Standardized uptake values of normal tissues at PET with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose: variations with body weight and a method for correction. *Radiology.* 1993;189:847–850.