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The Mammogram That Cried Wolfe

Karla Kerlikowske, M.D.

That mammographic density is an important risk factor for breast cancer was first recognized by Wolfe in the 1970s. His pioneering observation has since been confirmed in more than 42 studies, the vast majority of which have shown an association between increased mammographic density and the risk of breast cancer.[1] Women in the highest quartile of mammographic density have a risk of breast cancer that is approximately four to six times as high as that among women of similar age who are in the lowest quartile. Only two other factors increase the risk of breast cancer more than mammographic density: age and mutations in the breast cancer–susceptibility genes *BRCA1* and *BRCA2*.

Mammographic density is a function of the abundance of epithelial and connective tissue in the breast, but a cancer and these normal tissues can have a similar radiographic attenuation, which can make both appear radiodense or white on a mammogram. By contrast, fat is radiolucent or dark on a mammogram.[2,3] Therefore, it is possible that the risk associated with mammographic density is due to a masking effect — extensive breast density can hide a cancer.

In this issue of the *Journal*, Boyd et al.[4] suggest that a masking effect is likely in the short term after mammography among women with density in 75% or more of the breast, as measured by qualitative or semiquantitative methods. They calculated the odds of screen-detected breast cancer (defined as a breast cancer detected at the time of screening mammography) and of breast cancer detected by methods other than screening (defined as a breast cancer that was detected within 12 months after a negative screening examination) in relation to the extent of mammographic density. They found that the odds ratio of screen-detected breast cancer was 3.5 in women with extensive density as compared with women who had density in less than 10% of the breast. The masking effect greatly increased the odds of a cancer detected by nonscreening methods in women with extensive density as compared with those with density in less than 10% of the breast — odds ratio, 17.8.

The results of the study by Boyd et al. are similar to those of the Breast Cancer Surveillance Consortium, which reported that the rate of screen-detected breast cancer (defined as breast cancer detected within 12 months after a positive screening examination) is 2.5 times as high in women 40 to 49 years of age whose mammographic-density category was extremely dense as in women in the category called "almost entirely fat," according to the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) (Table 1). The rate of breast cancer not detected by screening mammography (defined as breast cancer detected within 12 months of a negative screening examination) is 15 times as high in women 40 to 49 years of age with a BI-RADS density of extremely dense as in women whose mammogram is in the almost-entirely-fat category. Rates of cancer not detected by screening mammography among women with extensive breast density increase with age and are highest in women 60 to 69 years of age. A large proportion of women 40 to 49 years of age who receive a diagnosis of breast cancer have extensive mammographic density, but the absolute risk of cancer among women in this age group who have extensive density is relatively low — even lower than that among older women with extensive density (Table 1).

Boyd et al. also report an association between

Table 1. Breast Cancer Surveillance Consortium Rates of Breast Cancer on Screening Mammography, According to BI-RADS Density Categories and Age, 1996 to 2003.*

Age at Screening	BI-RADS Density	Screening Examinations	Rate of Cancer Detected†	Rate of Cancer Not Detected‡
		no./total no. (%)	*no./1000 examinations*	
40–49 yr	Almost entirely fat	32,819/651,781 (5)	1.0	0.1
	Scattered fibroglandular densities	233,224/651,781 (36)	1.8	0.4
	Heterogeneously dense	300,464/651,781 (46)	2.5	0.9
	Extremely dense	85,274/651,781 (13)	2.5	1.5
50–59 yr	Almost entirely fat	51,608/645,561 (8)	1.5	0.1
	Scattered fibroglandular densities	289,783/645,561 (45)	3.4	0.6
	Heterogeneously dense	259,210/645,561 (40)	4.5	1.3
	Extremely dense	44,960/645,561 (7)	4.2	2.2
60–69 yr	Almost entirely fat	49,131/417,009 (12)	2.4	0.4
	Scattered fibroglandular densities	214,982/417,009 (51)	5.0	1.0
	Heterogeneously dense	136,794/417,009 (33)	6.4	1.7
	Extremely dense	16,102/417,009 (4)	5.3	3.0

* Data were provided by the Breast Cancer Surveillance Consortium (BCSC). The BCSC can be accessed at http://breastscreening.cancer.gov/. BI-RADS denotes American College of Radiology Breast Imaging Reporting and Data System. The BI-RADS categories are defined as almost entirely fat (<25% fibroglandular), scattered fibroglandular densities (25 to 50% fibroglandular), heterogeneously dense (51 to 75% fibroglandular), and extremely dense (>75% fibroglandular).
† Breast cancers were detected within 12 months after a positive screening mammographic examination.
‡ Breast cancers were detected within 12 months after a negative screening mammographic examination.

breast cancer and extensive mammographic density even when the density was observed as long as 8 years before a diagnosis of breast cancer, thus verifying the results of a previous study.[5] This finding indicates that the association between extensive mammographic density and an increased risk of breast cancer is due not only to a masking effect but also to a biologic connection between breast density and breast cancer. More research is needed to understand how breast density affects susceptibility to breast cancer; mammographic density is known to be influenced by genetic factors that may increase susceptibility to breast cancer more in younger women than in older women.

Extensive mammographic density is present in 25% of cases of breast cancer,[4] which suggests that measures of mammographic density could be useful in assessing the risk of breast cancer and in guiding measures to prevent breast cancer. Three models incorporate breast density into an assessment of risk for breast cancer. A simple prediction model for breast-cancer risk, based on the BI-RADS assessment of breast density alone and adjusted for age and race or ethnic group, is as accurate as the more complex Gail model of the National Cancer Institute.[6] The risk model of the Breast Cancer Surveillance Consortium shows that assessment of breast density according to BI-RADS is a statistically significant addition to the prediction of breast cancer in premenopausal and postmenopausal women.[7] An updated Gail model that includes a semiquantitative measure of breast density improves the discriminatory power of the model, as compared with the original model and with models that use BI-RADS categories of breast density.[6-8] Yet the ability to predict breast cancer accurately in an individual woman remains in question; all three risk models have only moderate predictive power, perhaps in part because measures of breast density are imprecise.

Measures of density according to BI-RADS categories of density are routinely included in mammography reports to practitioners, but they are only moderately reproducible between observers and between examinations rated by the same observer.[9,10] Semiquantitative measures that outline the breast and draw with computer guidance the

dense areas on digitized mammograms are time intensive, have an element of subjectivity, and require training, but they have better reproducibility than the qualitative measure reported by Boyd et al. In its current form, the semiquantitative method has not been integrated into routine mammography, because it requires acquiring, digitizing, and analyzing mammograms in a separate laboratory. Automated measures of the volume of density are under development and hold great promise in improving the accuracy and precision of measures of breast density and their applicability to clinical practice.[11]

Postmenopausal women rarely are assessed for the risk of breast cancer with the use of the Gail model, and they do not usually receive preventive therapy, even if they are at high risk for breast cancer.[12] A model for risk assessment that includes breast density that is used around the time of screening mammography would create an opportunity to discuss with a woman her risk of breast cancer during the next five years and to counsel her about prevention if she has a high risk. Clinicians could refer women with an estimated risk of breast cancer of 2% or higher for detailed risk assessment, counseling about modifiable risk factors, and the use of selective estrogen-receptor modulators to reduce the risk of breast cancer.

Should women with increased mammographic density be screened more often or with a different screening method than should other women? Digital mammography seems to detect more breast tumors in women with dense breasts than does film mammography.[3] There is, however, no evidence that deaths from breast cancer are reduced in women who undergo digital mammography. Nevertheless, early detection could provide benefits similar to those of film-screen mammography. If additional studies confirm that digital mammography detects more breast tumors in women with dense breasts than does film mammography, clinicians with limited access to digital machines will have to refer women with dense breasts for digital mammography. As noted by Boyd et al., increasing the frequency of screening is not likely to influence the rate of cancer detection among women with extensive density, because the tumors are not visible, because the tumors may grow quickly between examinations, or both.

In summary, increased mammographic density is strongly associated with increased susceptibility to breast cancer and decreased detection of cancer by mammography. Measures of breast density can be used in combination with other risk factors to determine a woman's risk of breast cancer.[7,8] Routine screening mammography could include an assessment of risk factors and a measurement of breast density, which together give a woman and her physician an estimate of her risk of breast cancer. Including risk assessment at the time of screening mammography could substantially increase the identification of high-risk women and provide an opportunity to consider pharmacologic and nonpharmacologic means to reduce their risk. The time has come to acknowledge breast density as a major risk factor for breast cancer and to determine, develop, and test the best ways to measure breast density in clinical practice and use this measurement to maximize primary and secondary prevention of breast cancer.

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The End of an Era in Otitis Research

Stephen Berman, M.D.

Retrospective studies carried out in the 1950s, 1960s, and 1970s suggested an association between otitis media early in life and subsequent developmental impairments in children. Although these studies were not designed to establish a cause-and-effect relationship, many prominent physicians, audiologists, and speech pathologists thought that a cause-and-effect relationship did exist, because severe, bilateral sensorineural hearing loss was known to cause irreversible developmental impairments. Therefore, aggressive intervention to restore normal hearing became the standard of care, and the placement of tympanostomy tubes became the second most frequent surgical procedure performed in the United States (after neonatal circumcision). In July 1994, the Agency for Health Care Policy and Research (now the Agency for Healthcare Research and Quality) published a clinical practice guideline that recommended the insertion of tympanostomy tubes when bilateral middle-ear effusion had persisted for 4 to 6 months with a hearing threshold of 20 dB or higher in otherwise healthy children 1 to 3 years of age.[1]

The article by Paradise et al. in this issue of the *Journal*[2] marks the final installment of reports from a longitudinal study that have led to a reappraisal of this practice. Recognizing the deficiencies of previous retrospective studies, Paradise and colleagues designed a prospective study to answer three key questions. First, is there an association between early otitis media and later impairments of speech, language, and cognitive development? Second, if an association exists, is it a cause-and-effect relationship? Third, if developmental impairments result from early otitis media, are they irreversible?[3]

From June 1991 through December 1995, the study enrolled 6350 healthy infants who were 2 to 61 days of age from eight sites in the greater Pittsburgh area serving families across the socioeconomic spectrum. The middle-ear status of these patients was monitored by means of pneumatic otoscopy and, in most instances, tympanometry at least monthly until 3 years of age in order to document the presence of a middle-ear effusion and identify a subgroup of patients who met specified criteria for the insertion of tympanostomy tubes. Children in the randomized trial underwent extensive developmental testing at 3, 4, 6, and 9 to 11 years of age. During the course of the follow-up period, the domains assessed included parental stress and the children's behavior, psychosocial development, language, speech, intelligence, attention, and academic achievement. Among the study participants, 429 children with bilateral middle-ear effusion lasting for 90 days or unilateral middle-ear effusion lasting for 135 days were randomly assigned to receive tympanostomy tubes promptly or up to 9 months later if the effusion persisted. If a causal relationship exists between persistent effusion and developmental impairments, the test scores of the children receiving tympanostomy tubes earlier should have been better than the scores of the children with tubes placed later in life.

In addition, a representative sample of 241 children selected from those who were ineligible for randomization underwent similar developmental assessments. This observational component of the study was included to determine whether the association between early otitis media and later developmental impairments remained when the effects of potentially confounding demographic variables were considered.

In previous reports on assessments at 3, 4, and 6 years of age, no significant differences were found in the test scores for any of the outcomes between the children who received tympanostomy tubes early in life and those who received