

Short communication

Mammographic density

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Introduction

The present short review will address three questions: What is the evidence that breast density is a major risk factor for breast cancer? How is breast density best assessed and what factors influence breast density? How do you utilize breast density in the preventative setting?

What is the evidence that breast density is a major risk factor for breast cancer?

McCormack and dos Santos Silva have reviewed the data on the association of percentage mammographic density (PMD) with risk of breast cancer in a systematic meta-analysis of data for >14,000 cases and 226,000 noncases from 42 studies [1]. They found that PMD was consistently associated with risk of breast cancer. Associations were stronger in studies in the general population, rather than in symptomatic women, for percentage density rather than for Wolfe categories, and in studies of incident cancer rather than prevalent cancer. The breast cancer risk associated with density did not differ by age, menopausal status or ethnicity and cannot be explained by the masking of cancers by dense tissue [2].

A total of 10 cohort studies have been reported to date, all carried out as case-control studies nested within cohorts that used quantitative methods to classify PMD [2-10]. The interval between the mammogram used to classify PMD and the date of diagnosis of breast cancer varied from 1 year to 10 years. Methods of classifying PMD in analysis varied among these studies, but all showed a substantial increase in breast cancer risk across over the partitions of PMD examined, with most odds ratios being between 4 and 5. PMD is associated with a risk of breast cancer at screening and between screening examinations [2,11].

Mammographic density expressed as either a percentage of the area of the breast (PMD) or as the area of dense tissue

(cm²) in a mammogram are both positively associated with risk of breast cancer, but PMD is the stronger association [5].

Conclusions

PMD has a consistent strong influence on breast cancer risk, is independent of other risk factors, has a larger gradient in risk than most other risk factors, has an increased risk that extends for at least 10 years after the mammogram used to classify density, and carries a risk not explained by masking.

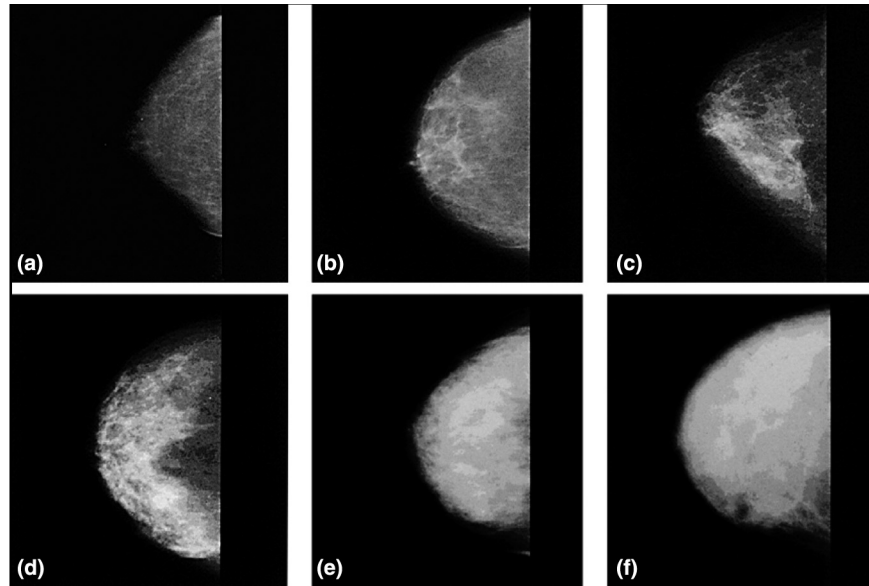
How is breast density best assessed and what factors influence breast density?

Measurement

Examples of mammographic density of varying extents are shown in Figure 1. Four principal methods have been used to date to assess mammographic density. First, Wolfe described four categories of density: N1, predominately fat; P1 and P2, ductal prominence in, respectively, <25% or >25% of the breast; and DY, extensive dysplasia [12,13]. The Breast Imaging Reporting and Data System (BI-RADS) also has four categories: 1, predominately fat; 2, scattered densities; 3, heterogeneously dense; and 4, extremely dense [14]. The third method involves visual estimation of the proportion of the breast occupied by radiologically dense breast tissue [15]. Finally, there are computer-assisted methods of measurement (Cumulus and other similar programs) based on interactive thresholding [16]. Cumulus is illustrated in Figure 2. An observer places thresholds at the edge of the breast (red line) and at the edge of the density (green line), and the areas so defined are recoded by the computer. PMD is calculated by dividing the dense area by the total area times 100 and can be treated in analysis as either a continuous variable or a categorical variable.

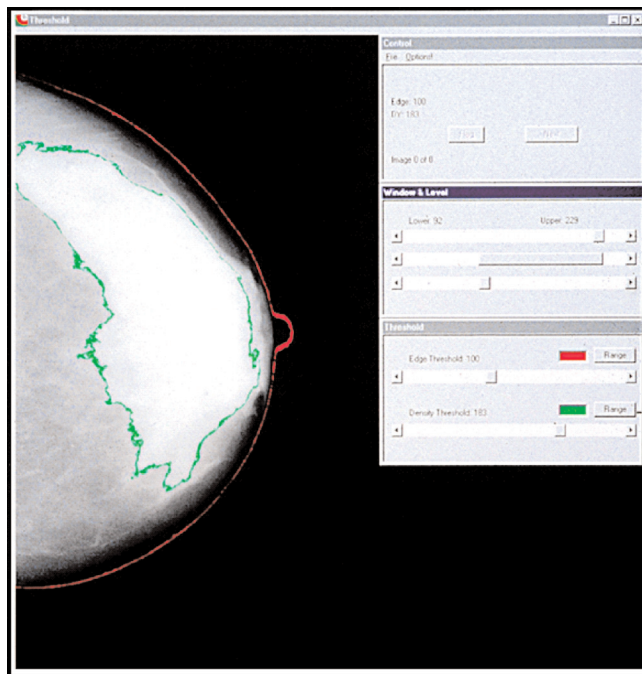
These methods differ in their ease of application and in their reliability. The Wolfe categories have largely been replaced in the literature by quantitative methods of classification or by

Figure 1



Examples of mammographic density. (a) 0%. (b) <10%. (c) <25%. (d) <50%. (e) <75%. (f) >75%.

Figure 2



Computer-assisted measurement of mammographic density.

measurement has been used mostly in research studies as it requires a trained observer and digitized film images, or processed images from digital mammography. Reliability between readers in the use of these methods is modest for BI-RADS ($\kappa \sim 0.6$) [17], intermediate for quantitative estimation by a radiologist (intraclass correlation coefficient ~ 0.7) [15] and good for Cumulus (intraclass correlation coefficient ~ 0.9 or greater) [2].

All current methods of assessment use only the two dimensions of the mammogram, and none take into account variations in image production or processing. Despite this, the methods have all been shown to have an association with risk of breast cancer. Quantitative methods are more time consuming than are qualitative methods, and require a trained observer and digitized images, but are more reliable and can provide information about the separate components of the ratio of percentage density.

Conclusions

All current methods of assessing density have advantages and disadvantages, and no method is ideal. All methods have measurement error. The breast cancer risk associated with density may be substantially underestimated. Densities on digital and film mammograms are not identical.

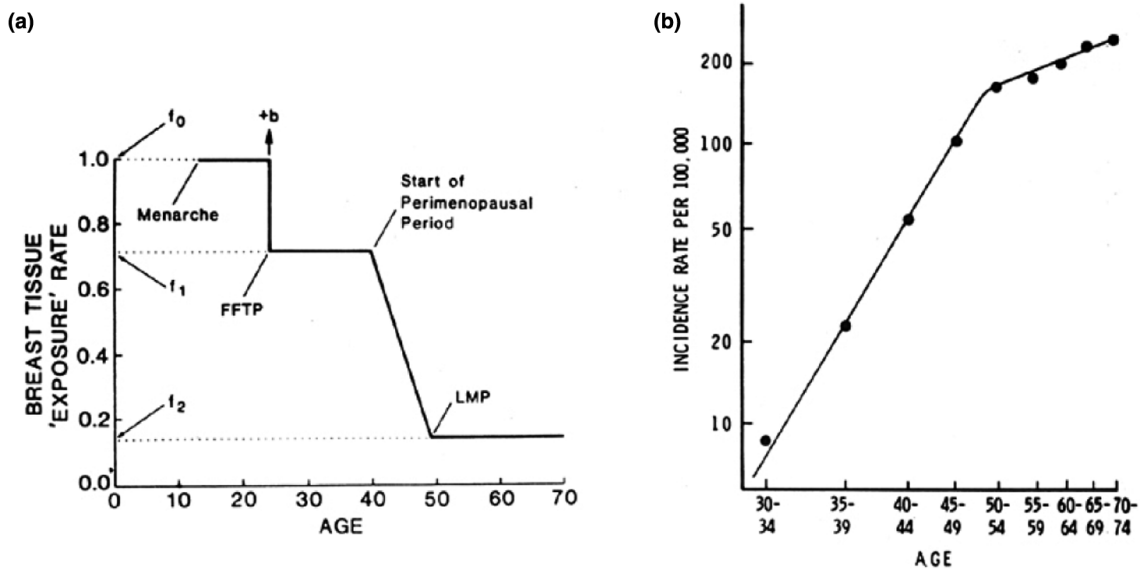
Influences

Age, mammographic density and incidence of breast cancer

The distribution of PMD changes with increasing age [5,18,19], reflecting the reduction in glandular tissue and accompanying increase in fat that occurs with increasing age

the BI-RADS score, which is completed in a large proportion of routine mammograms in the USA. Quantitative assessment of mammograms using Cumulus or other similar methods of

Figure 3



(a) Pike model of mammary carcinogenesis. (b) Age-specific incidence of breast cancer – observed and predicted by the Pike model. Reprinted by permission from Macmillan Publishers Ltd: Pike and colleagues, *Nature* © 1983 [21].

[20]. The decline in density with age may seem paradoxical, as breast cancer incidence increases with age, but this apparent paradox may be resolved by reference to a model of breast cancer incidence proposed by Pike and colleagues [21]. The model is based on the concept that breast tissue age, or breast tissue exposure rather than chronological age, is the relevant measure for describing the incidence of breast cancer. Breast tissue age is closely associated with exposure of breast tissue to hormones and growth factors, and to the effects that menarche, pregnancy and menopause have on these exposures and on susceptibility to carcinogens. As shown in Figure 3, breast tissue exposure is greatest at the time of menarche, falls with pregnancy, is further reduced in the perimenopausal period, and is least after the menopause. Pike and colleagues showed that cumulative breast tissue exposure, given by the area under the curve in Figure 3a, describes the age–incidence curve for breast cancer shown in Figure 3b.

Breast cancer risk factors

As further described below, average PMD is reduced with increasing age [19]. PMD is also less extensive in women who are parous, less extensive in those with a larger number of live births [22,23], and is reduced by menopause [18,24,25]. After adjustment for age and other potential influences, a family history of breast cancer is associated with more extensive PMD [26]. PMD has consistently been found to be inversely associated with body weight [27,28], and greater birth weight and adult height are positively associated both with PMD [27,29] and with an increased risk of breast cancer [30-33].

Factors that change mammographic density

Combined hormone therapy, but not estrogen alone, is associated with an increase in risk of breast cancer [34] and an increase in PMD [35,35-37]. PMD in postmenopausal women is reduced by tamoxifen [38] and raloxifene [39], drugs that reduce breast cancer incidence, and PMD in premenopausal women is reduced by a gonadotrophin-releasing hormone agonist [40]. Cuzick and colleagues, in a study published to date only in abstract form, have reported an association between a reduction in PMD following use of tamoxifen and reduction in breast cancer incidence [41]. The clinical or biological significance of any given change in PMD is currently unknown.

Heritability

The breast cancer risk factors whose influence was described above account for only 20 to 30% of the variation in PMD observed in the population [24], and genetic factors might explain some of the unexplained variation of PMD. In collaboration with John Hopper (Melbourne, Australia) we carried out two twin studies of substantial size to estimate the proportion of the variance in PMD that could be explained by genetic factors [42]. Mammograms were obtained in 951 twin pairs aged 40 to 70 years, in Australia and North America, and information was collected on the factors associated with variations in PMD. Details of the findings are given in [42]. The proportion of the residual variation in PMD accounted for by additive genetic factors (heritability) was estimated to be 60% (95% confidence interval = 54 to 66%) from Australian twins, 67% (95% confidence interval = 59 to 75%) from North American twins, and 63% (95% confidence

interval = 59 to 67%) in the combined studies [42]. These data thus provide an almost exact replication of evidence that is consistent with a strong genetic influence on PMD. A subsequent study with 553 twin pairs found similar results [43]. PMD thus has the characteristics of a quantitative trait.

Conclusions

The association of density with age resembles Pike and colleagues' log-incidence breast tissue exposure model. Mammographic density is influenced by several factors, including drugs that influence the risk of breast cancer. The genetic influence is stronger than that of other risk factors.

How do you use breast density in the preventive setting?

The ability to predict the future occurrence of disease in individuals allows the improved design and application of preventive strategies, improved planning of intervention trials, revision of the risks and benefits associated with preventive interventions, and improved clinical decision-making [44]. Cardiovascular medicine provides a paradigm for an approach to disease prevention based on risk prediction, and modification of risk factors has been estimated to account for approximately one-half of the 40% reduction in age-specific mortality from cardiovascular disease observed over the past three decades, the remainder of the reduction being attributed to improvements in treatment [45].

Prediction of the risk of developing breast cancer is less well developed than for cardiovascular disease [44]. The most widely used current method of predicting risk of breast cancer is the Gail model [46], which includes age, age at menarche, age at first live birth, number of previous benign breast biopsies, and number of first-degree relatives with breast cancer.

The addition of PMD (described by the BI-RADS method) to the Gail model increased the concordance statistic from 0.607 to 0.642, more than did the addition of the seven SNPs found reproducibly to be associated with breast cancer (concordance statistic = 0.632). These levels of individual prediction are no better than modest.

Conclusions

Individual risk prediction using PMD is modest, with or without other risk factors. Group risk prediction may be useful in trial design. Mammographic density has not yet been shown to meet criteria for surrogacy in any setting.

Future research

Research in progress in several centers can be expected in the next few years to identify the genetic variants associated with differences in PMD [47]. Events in early life are believed to have an important influence on later risk of breast cancer [48], and research into the factors that influence breast development and breast tissue composition in early life may

provide insight into more effective methods of breast cancer prevention [49]. Despite the recognized importance of PMD as a risk factor for breast cancer, we still lack reliable, automated, quantitative and volumetric methods of measuring this risk factor – the development of such methods should be a high priority.

Competing interests

The authors declare that they have no competing interests.

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